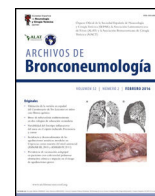




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Scientific Letter

Macrolide-based Treatment and Long-term Outcomes in Community-acquired Pneumonia

To the Editor,

Current clinical guidelines for the management of hospitalised community-acquired pneumonia (CAP) recommend either a combination of a beta-lactam with a macrolide or monotherapy with a fluoroquinolone. In patients with severe disease, a beta-lactam plus a macrolide regimen has shown better short outcomes [1]. However, no clear preference is established between these strategies in non-severe CAP [2]. Antibiotic selection is guided by evidence of short-term clinical efficacy; nevertheless, the long-term impact of antibiotics administered during the acute phase of CAP remains insufficiently understood [3].

Previous studies have consistently shown that, in patients with severe CAP, macrolide therapy in addition to beta-lactams is associated with reduced short-term mortality [4,5], likely related to their anti-inflammatory and host-response-modulating effects [6]. Recent data from a large cohort of severe CAP ($n = 3775$) suggest that macrolide-based treatment may also reduce 12-month mortality, indicating a potential benefit beyond the acute phase [7]. Whether this effect extends to non-severe CAP remains unknown.

Although macrolide use has been linked to an increased risk of short-term cardiovascular events (CVE) [8–10], epidemiological studies show inconsistent results, reflecting differences in study design and follow-up duration [11,12]. In elderly CAP patients treated with azithromycin, a modest increase in 30-day myocardial infarction risk has been reported despite overall survival benefit [13]. However, evidence on the cardiovascular impact beyond the early period, particularly up to one-year post-discharge, remains limited, and a recent meta-analysis found no association between clarithromycin use and long-term cardiovascular mortality [14].

The aim of this study is to evaluate the long-term risk of developing CVE or death within one year after hospital discharge in patients who received a macrolide-based treatment during hospitalization for CAP.

We performed a post-hoc analysis of the prospective multicentre NEUMONAC cohort [15], which included immunocompetent adults (≥ 18 years) discharged alive after hospitalisation for CAP. The study was approved by the Biomedical Research Ethics Committee of Hospital La Fe (2013/0204), and written informed consent was obtained from all participants. Patients were classified into macrolide-based or non-macrolide-based treatment groups according to in-hospital antibiotic administration. Those who received azithromycin or clarithromycin for at least two consecutive days as part of combination therapy, in accordance with Spanish clinical guidelines, were included in the macrolide group.

One-year follow-up was conducted through electronic health records and telephone interviews. The primary outcomes were CVE and all-cause mortality within one year. CVE included acute coronary syndrome, heart failure, arrhythmia, stroke, or venous thromboembolism, as previously defined [16].

Statistical analyses were conducted in R (v4.5.1) using the *brms* and *MatchIt* packages. Continuous variables were summarised as medians (interquartile range [IQR]), and categorical variables as counts (%). The association between in-hospital macrolide use and one-year CVE or mortality was evaluated using Bayesian multivariable logistic regression models adjusted for demographic and clinical covariates (age, sex, nursing home, previous comorbidities [hypertension, dyslipidaemia, diabetes, chronic pulmonary, renal and heart diseases], intensive care unit [ICU] admission, need of ventilation and initial severity [SpO₂/FiO₂ and CURB-65]). Estimates (odds ratio [OR]) were reported with 95% credible intervals (CrI) and probability of direction (pd) as a measure of effect existence [17]. A propensity score-matched analysis, using nearest-neighbour matching, was performed as a sensitivity analysis.

A cohort of 2180 patients was enrolled. A total of 1580 patients were included in the long-term analysis after excluding in-hospital deaths ($n = 108$), missing antibiotic data ($n = 15$), incomplete records ($n = 311$), or lack of one-year follow-up ($n = 166$). Of these, 509 (32.2%) received macrolide-based therapy (93% azithromycin and 7% clarithromycin) for a median of 4 (3–6) days. Baseline characteristics stratified by macrolide-based treatment status are summarised in Table 1.

Bayesian multivariable models show a high probability that macrolide use is associated with an increased risk of long-term cardiovascular complications after discharge (OR = 1.73, 95% CrI [1.17–2.56], probability of effect 99.6%). In addition, longer macrolide treatment duration shows a high probability of increased cardiovascular risk (OR = 1.10, 95% CrI [1.02–1.21], probability of effect 99.4%), with a monotonic effect observed. In contrast, the probability of a protective effect on mortality is moderate but not conclusive (OR = 0.70, 95% CrI [0.38–1.23], probability of effect 88.9%), with a similar pattern observed for treatment duration (OR = 0.91, 95% CrI [0.75–1.04], probability of effect 91%). In Fig. 1, the association between the duration of macrolide treatment and the risk of long-term CVE or mortality is shown.

Using propensity score matching, the findings are consistent with those obtained from the multivariable models. For CVE, the OR is 1.41 (95% CrI [0.92, 2.16], probability of effect 93.7%), and for mortality, the OR is 0.94 (95% CrI [0.50, 1.76], probability of effect 56.9%).

Our study shows that macrolide administration in patients hospitalised for CAP is associated with a greater probability of

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Table 1
Characteristics of study participants before and after propensity score matching.

	CAP patients with macrolide-based treatment (n = 509)	CAP patients without macrolide-based treatment (n = 1071)
Age, years, median (IQR)	69 (53, 79)	70 (55, 80)
Male sex, no. (%)	307 (60.3)	647 (60.4)
Coexisting conditions, no. (%) or median (IQR)		
AH	208 (40.9)	395 (36.9)
Dyslipidemia	155 (30.5)	296 (27.6)
Diabetes	119 (23.4)	236 (22.0)
Chronic pulmonary disease	143 (28.1)	254 (23.7)
Chronic heart disease	141 (27.7)	291 (27.2)
Chronic renal disease	41 (8.1)	75 (7.0)
Nursing home	23 (4.5)	44 (4.1)
Severity		
SpO ₂ /FiO ₂ at admission, median (IQR)	438.1 (407.6, 452.4)	438.1 (406.2, 452.4)
CURB-65 score, median (IQR) or no (%)	1 (1, 2)	1 (1, 2)
CURB-65 0–2	437 (85.9)	894 (83.5)
CURB-65 3–5	72 (14.1)	177 (16.5)
In-hospital outcomes, no. (%)		
NIMV or IMV	43 (8.5)	83 (7.8)
ICU-admission	50 (9.8)	123 (11.5)
In-hospital CVE*	31 (6.1)	103 (9.6)
Arrhythmia	14	67
Heart failure	18	34
Acute coronary syndrome	3	6
Stroke	0	2
Venous thromboembolism	0	4
Long-term outcomes, no (%)		
1-Year mortality	20 (3.4)	57 (5.3)
1-Year CVE*	53 (10.4)	67 (6.3)
Arrhythmia	24	34
Heart failure	21	31
Acute coronary syndrome	8	8
Stroke	0	0
Venous thromboembolism	0	1

CAP: community-acquired pneumonia; IQR: interquartile range; AH: arterial hypertension; SpO₂/FiO₂: peripheral blood oxygen saturation/fraction of inspired oxygen; NIMV: non-invasive mechanical ventilation; IMV: invasive mechanical ventilation; ICU: intensive care unit; CVE: cardiovascular events.

* Individual patients may have experienced more than one cardiovascular event.

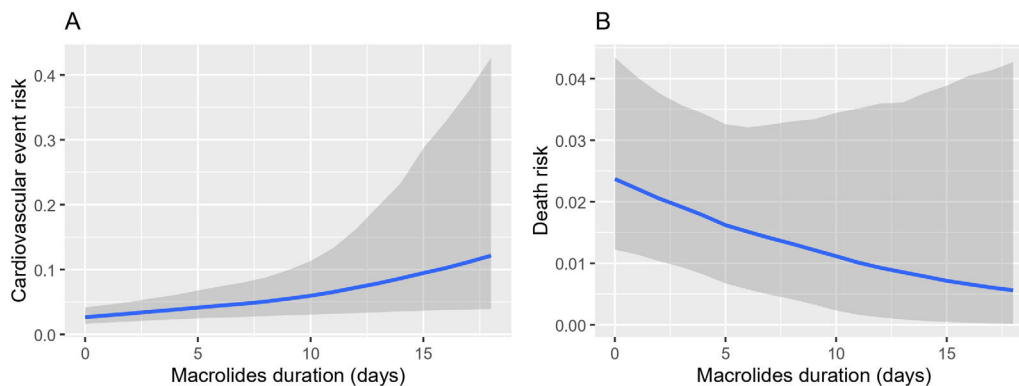


Fig. 1. Association between macrolide treatment duration (days) and long-term risk of CVE and mortality. (A) CVE and (B) mortality. Risk is shown as a proportion from 0 to 1.

developing CVE from discharge up to one year of follow-up. In addition, treatment duration appears to influence this probability, with longer courses associated with a higher likelihood of events. The pathophysiological mechanisms underlying this increased risk are not fully understood or known. These CVE occur even after treatment has been finalised, which may be related to macrophage activation leading to persistent inflammation and potential destabilisation of atheromatous plaques. Moreover, persistent inflammation may contribute to ventricular arrhythmogenesis and QT interval prolongation, potentially mediated by cytokine-induced inhibition of cardiac ion channels

(e.g., hERG potassium channels) or indirect effects on autonomic balance and myocardial repolarization [18]. These mechanisms could partly explain the observed clinical outcomes; however, further studies are needed to explore this point [8]. Previous studies have linked longer clarithromycin treatment duration – particularly beyond seven days – with an increased risk of CVE, suggesting that extended macrolide therapy may contribute to long-term cardiovascular complications [3]. Current guidelines and recommendations underline the value of shorter antibiotic courses, which offer therapeutic benefits and reduce adverse effects, thereby promoting responsible antibiotic use [2,19]. Even shorter courses may

be appropriate for macrolides due to their pharmacokinetic properties.

In our cohort, macrolide treatment consisted predominantly of azithromycin, with clarithromycin used in a smaller proportion of cases. Most of the available literature refers exclusively to clarithromycin use, although in Europe there is a growing trend towards increased azithromycin use over other macrolides [20]. Our findings indicate that azithromycin shows similar results to those reported for clarithromycin in relation to long-term cardiovascular events and mortality.

Our study indicates a moderate probability of a protective effect of macrolide use on long-term mortality; however, the data are not conclusive potentially attributable to limited statistical power. Other population-based studies have reported similar findings for in-hospital and post-discharge mortality [21,22].

The main strength of our study is the large multicentre cohort, with an additional analysis using propensity score matching, and the inclusion of macrolide therapy with both azithromycin and clarithromycin administered for more than two days. The principal limitation of our study stems from its observational design and post-hoc analysis. The results warrant confirmation in future clinical trials. Future prospective studies should incorporate randomised treatment allocation, systematic assessment of baseline cardiovascular risk factors, and predefined cardiovascular safety endpoints to mitigate bias. Another limitation of this study is that baseline cardiovascular risk could not be assessed using validated risk scores (e.g., SCORE2 or SCORE2-OP). Nevertheless, the analysis was adjusted for comorbidities with a well-established association with cardiovascular risk in order to distinguish whether the increase in cardiovascular events was driven by a higher underlying cardiovascular risk or by macrolide-based treatment. Finally, the study focuses on macrolide therapy in hospitalised CAP patients and does not include those treated as outpatients; however, since the mechanisms of cardiovascular risk associated with macrolides use are not expected to differ fundamentally in less severe cases, the findings may still provide insights for broader populations. Future studies in outpatient settings are recommended to confirm these observations. These findings advocate for the responsible and short use of macrolides, aligned with clinical guideline recommendations, in patients with CAP, in order to reduce the risk of poor outcomes not only in the acute phase but also in the longer term.

CRedit authorship contribution statement

Conceptualization and study design: P.G.-J., M.P., Ro.M., Ra.M. Patient enrolment: P.G.-J., M.P., A.L., Ra.M., N.M., L.M., C.M. Statistical analysis: D.H., P.G.-J., M.P., Ra.M. Drafting the manuscript: P.G.-J., M.P., Ra.M. Revision of manuscript and approval of the final version: all authors. P.G.-J. and M.P. are the guarantors.

Ethics approval and consent to participate

This study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the Biomedical Research Ethics Committee Hospital La Fe (2013/0204). All participants provided written informed consent. Clinical trial number: not applicable.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (GPT-5) in order to perform grammar corrections. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Conflict of interests

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

The data that supports the findings of this study are available from the corresponding author, upon reasonable request.

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