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A Hypothesis-Generating Study of the Combination of Aspirin plus Macrolides in Patients with Severe Community-Acquired Pneumonia

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ABSTRACT While the inflammatory response to severe pneumonia is paramount in limiting and resolving the infection, excessive inflammation can lead to deleterious effects. We theorized that patients with severe community-acquired pneumonia (CAP) who were treated with macrolides and aspirin would receive benefit beyond that of conventional antibiotic therapy. An observational study was conducted with patients with severe CAP. All patients were admitted to 5 teaching hospitals (in Italy, the United States, Japan, and China), and data were gathered from their electronic medical records. Severe pneumonia was defined according to Infectious Diseases Society of America/American Thoracic Society criteria. Patients were divided into 4 groups, i.e., (i) the aspirin-only group (ASG), (ii) the macrolide-only group (MG), (iii) the aspirin plus macrolide group (ASMG), or (iv) the neither aspirin nor macrolide group (NASMG). Survival rates for the 4 groups were evaluated after adjustment for confounders and after weighting by propensity score. A total of 1,295 patients were included in the analysis. There were 237 patients (18.3%) in the ASG, 294 (22.7%) in the MG, 148 (11.4%) in the ASMG, and 616 (47.6%) in the NASMG. The mortality rate at 30 days was 15.5% in the ASMG, compared to 28.2% in the NASMG, 23.8% in the MG, and 21.1% in the ASG. After propensity score analysis, receipt of aspirin plus macrolide (hazard ratio, 0.71 [95% confidence interval, 0.58 to 0.88]; $P = 0.002$) was associated with a higher 30-day survival rate. This is a hypothesis-generating study in which data suggest that the combination of aspirin plus a macrolide improves 30-day survival rates for patients with severe CAP. Further randomized studies will need to be undertaken to confirm this phenomenon.

KEYWORDS aspirin, community-acquired pneumonia, macrolides, septic shock, severe pneumonia

Community-acquired pneumonia (CAP) is the most common type of infection leading to hospitalization in intensive care units (ICUs) and the most common cause of death associated with infectious diseases (1–3). Despite the advances in

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antimicrobial therapy and the improvements in intensive care medicine, diagnosis of severe pneumonia is associated with mortality rates as high as 50% (4, 5).

The high mortality rates observed for patients with severe pneumonia are related to the development of sepsis and/or septic shock; the disease progression is associated with an overwhelming inflammatory reaction, and it has been suggested that the use of agents that interfere with the pathogenesis of sepsis by modulating inflammation and coagulation, including agents with anti-inflammatory properties, such as macrolides, steroids, aspirin, statins, or others (6, 7), may hamper that process. Different meta-analyses showed that the addition of a macrolide antibiotic to a β -lactam reduced mortality rates for patients with severe CAP (8, 9). A retrospective study also suggested that macrolide use was associated with reduced mortality rates for septic patients with pneumonia due to macrolide-resistant pathogens (10); more recently, the use of a modified macrolide lacking antibiotic activity but retaining anti-inflammatory properties dramatically improved the survival rates for levofloxacin-treated mice with *Pseudomonas aeruginosa* respiratory infections (11). Moreover, experimental studies demonstrated that lungs of infected mice are massively infiltrated by aggregates of activated platelets and activation of protease-activated receptor 4, a platelet receptor for thrombin, exacerbates influenza-induced acute lung injury and promotes death (12). Low-dose aspirin, which inhibits platelet aggregation through irreversible acetylation of cyclooxygenase 1 (COX1), has been associated with improved survival rates for patients with CAP (13). Since limited clinical data exist regarding the prognostic role of macrolide and aspirin therapy for patients with severe CAP, we aimed to evaluate the possible role of the combination of aspirin plus a macrolide in a large multinational cohort, to generate a hypothesis to support eventual randomized trials.

RESULTS

During the study period, a total of 1,295 patients with severe CAP were included. Overall, the 30-day mortality rate was 24.4%. Baseline characteristics of the population are reported in the supplemental material (see Table S1 at <https://www.alariconetwork.com/novita-scientifiche>). The distribution of patients in the 4 study groups was as follows: 237 patients (18.3%) received only aspirin, 294 patients (22.7%) received only a macrolide, 148 patients (11.4%) received a combination of aspirin plus a macrolide, and 616 patients (47.6%) received neither aspirin nor a macrolide (Fig. 1). For all patients in the aspirin groups, prehospital use of aspirin before the pneumonia event was reported.

Demographic, anamnestic, and clinical characteristics of the patients with severe pneumonia in the 4 study groups are reported in Table 1. All patients belonged to the higher-risk classes, based on pneumonia severity index (PSI) and CURB-65 scores; patients in the aspirin-only group (ASG) showed a higher frequency of ≥ 2 comorbidities (63.3%), while a multidrug-resistant (MDR) etiology (22.2%) was more frequently reported in the neither aspirin nor macrolide group (NASMG). Table S2 in the supplemental material at <https://www.alariconetwork.com/novita-scientifiche> reports pathogens isolated from 373 patients with culture-positive severe pneumonia.

Radiological features, laboratory findings, and outcomes for patients with severe pneumonia in the 4 study groups are presented in Table 2. A higher incidence of cardiovascular events during hospitalization was observed in the ASG (23.2%), while the use of inotropic agents (37.1%) and septic shock (39.2%) were more frequently observed in the aspirin plus macrolide group (ASMG). Patients in the NASMG had the higher 30-day mortality rate (28.2%), followed by the macrolide-only group (MG) (23.8%), the ASG (21.1%), and the ASMG (15.5%). Inclusion in the ASMG was associated with improved outcomes in comparison to the NASMG ($P = 0.001$) and the MG ($P = 0.04$) but not in comparison to the ASG ($P = 0.12$).

Cox regression analysis after propensity score weighting showed that the use of aspirin plus a macrolide in combination was associated with an increased 30-day survival rate (hazard ratio [HR], 0.71 [95% confidence interval [CI], 0.58 to 0.88]; $P = 0.002$). The HRs for 30-day deaths among the 4 study groups are reported in Fig. 2.

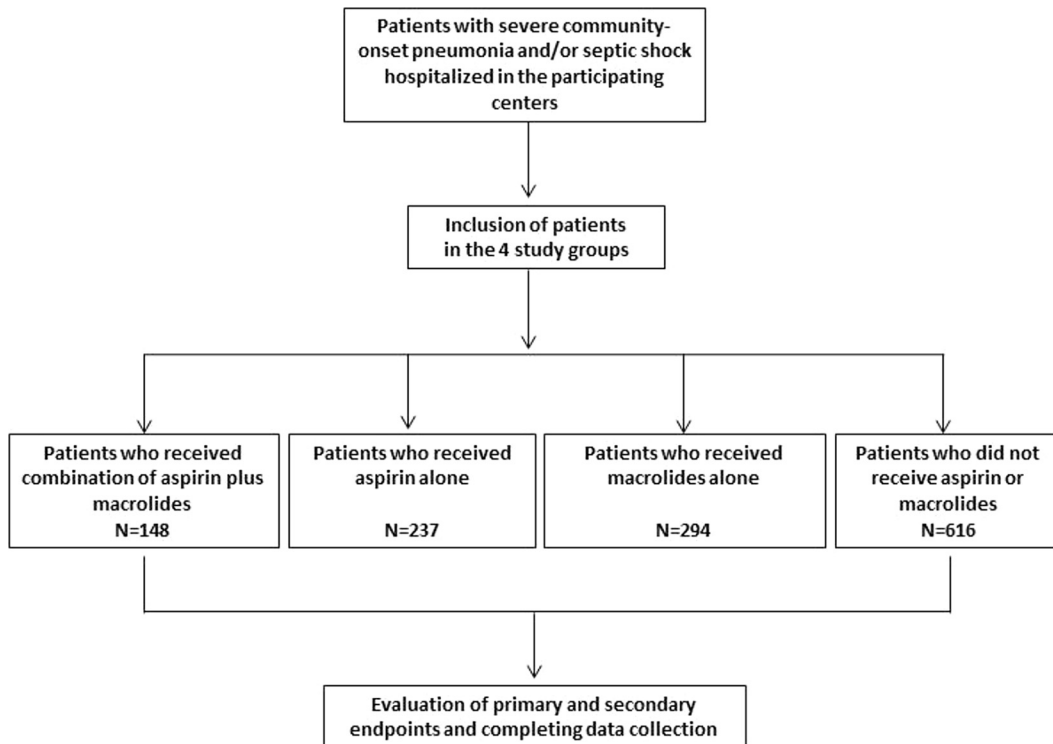


FIG 1 Flow chart for the study.

The use of aspirin plus a macrolide in combination showed a protective effect in comparison to findings for the NASMG (HR, 1.39 [95% CI, 1.12 to 1.71]; $P = 0.002$) and the MG (HR, 1.54 [95% CI, 1.24 to 1.9]; $P < 0.001$), while there was no significant effect in comparison to findings for the ASG (HR, 1.185 [95% CI, 0.95 to 1.47]; $P = 0.122$). Kaplan-Meier curves for 30-day survival rates for the 4 study groups are reported in Fig. 3. Propensity score-weighted survival curves are reported in Fig. S1 at <https://www.alariconetwork.com/novita-scientifiche>. The balancing properties of our model are reported in Table S3 at <https://www.alariconetwork.com/novita-scientifiche>.

DISCUSSION

Our study suggests that, for patients with severe CAP, the combination of low-dose aspirin (≥ 100 mg/day) plus a macrolide is associated with improved 30-day survival rates. To our knowledge, this is the first study demonstrating, in a large cohort of patients, the role of these drugs in combination for patients hospitalized in the emergency department with severe pneumonia.

Antibiotic therapy alone may not be sufficient to reduce mortality rates for septic patients with pneumonia. After the initial administration of effective antibiotic therapy, most bacteria are killed within the first 24 h of therapy (14) but, despite a marked reduction or clearance of the bacterial inoculum, the progression to sepsis or septic shock may eventually ensue until death, and antibiotic therapy alone may not be sufficient to halt this process. Macrolides and aspirin are drugs with well-recognized anti-inflammatory effects. Macrolides have multiple immunomodulatory effects, and long-term use of macrolides has been associated with increased survival rates in various lung diseases characterized by chronic airway inflammation, such as cystic fibrosis and asthma (15). A recent study using a mouse model showed that, in lethal pneumococcal pneumonia, macrolides can restore immune functions (16). Moreover, clinical studies conducted with patients admitted to the ICU with severe CAP identified macrolide use as a factor associated with lower ICU mortality rates (17). Similarly, the administration of clarithromycin has been associated with restoration of the balance between proin-

TABLE 1 Demographic and clinical features of patients with severe pneumonia in the 4 study groups

Variable ^a	ASMG (n = 148)	ASG (n = 237)	MG (n = 294)	NASMG (n = 616)	P ^b
Baseline characteristics					
Age (median [IQR]) (yr)	79 (69–82)	79 (68–81)	75 (69–82)	76 (68–82)	<0.001
Male (no. [%])	94 (63.5)	156 (65.8)	173 (58.8)	386 (62.6)	0.41
≥2 comorbidities (no. [%])	82 (55.4)	150 (63.3)	133 (45.2)	277 (44.9)	<0.001
Charlson Comorbidity Index (median [IQR])	3 (1–5)	3 (1–5)	3 (1–5)	3 (1–5)	0.51
Chronic heart disease (no. [%])	54 (36.4)	93 (39.2)	56 (19)	136 (22.1)	<0.001
Chronic liver disease (no. [%])	3 (2)	11 (4.6)	11 (3.7)	38 (6.1)	0.13
Diabetes mellitus (no. [%])	54 (36.4)	82 (34.6)	52 (17.7)	132 (21.4)	<0.001
Neoplasm (no. [%])	24 (16.2)	31 (13.1)	59 (20)	159 (25.8)	<0.001
Chronic renal failure (no. [%])	37 (25)	50 (21.1)	34 (11.5)	86 (13.9)	<0.001
Hemodialysis (no. [%])	5 (3.3)	15 (6.3)	5 (1.7)	15 (2.4)	0.007
COPD (no. [%])	32 (21.6)	62 (26.1)	72 (24.5)	104 (16.8)	0.006
PPI/H ₂ blocker (no. [%])	76 (51.3)	141 (59.5)	139 (47.3)	283 (45.9)	<0.001
Previous antibiotic therapy (30 days) (no. [%])	22 (14.8)	43 (18.1)	75 (25.5)	169 (27.4)	0.004
Immunosuppressive therapy (no. [%])	25 (16.9)	50 (21.1)	74 (25.1)	123 (19.9)	0.21
LTCF (no. [%])	6 (4)	21 (8.8)	26 (8.8)	66 (10.7)	0.29
Clinical features and disease severity					
Delirium at pneumonia onset (no. [%])	34 (23)	78 (32.9)	75 (25.5)	247 (40.1)	<0.001
Tachypnea (≥30 breaths/min) (no. [%])	42 (28.3)	94 (39.6)	116 (39.4)	222 (36)	0.88
Fever (no. [%])	88 (59.4)	97 (40.9)	133 (45.2)	292 (47.4)	0.004
CVC (no. [%])	21 (14.2)	61 (25.7)	62 (21.1)	89 (14.4)	<0.001
Bacteremia (no. [%])	31 (20.9)	81 (34.1)	62 (21.1)	151 (24.5)	0.006
Glasgow Coma Scale score (median [IQR])	11 (3–13)	14 (5–15)	14 (4–15)	13 (3–15)	<0.001
PSI class IV (no. [%])	44 (29.7)	60 (25.3)	76 (25.8)	182 (29.5)	0.45
PSI class V (no. [%])	87 (58.8)	130 (54.8)	152 (51.7)	322 (52.2)	0.26
CURB-65 class II (no. [%])	51 (34.4)	53 (22.3)	60 (20.4)	170 (27.6)	0.008
CURB-65 class III (no. [%])	74 (50)	128 (54)	146 (49.6)	326 (52.9)	0.25
Septic shock (no. [%])	58 (39.2)	61 (25.7)	61 (20.7)	182 (29.5)	<0.001

^aIQR, interquartile range; PSI, pneumonia severity index; LTCF, long-term-care facility; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; CVC, central venous catheter; ASMG, aspirin plus macrolide group; ASG, aspirin-only group; MG, macrolide-only group; NASMG, no aspirin or macrolide group.

^bDescriptive *P* values for the nonparametric ANOVA/chi-square hypothesis that ≥1 group differs from the others.

flammatory and anti-inflammatory mediators in patients with ventilator-associated pneumonia (VAP) (18).

Aspirin has several anti-inflammatory activities (19). It is able to inhibit platelet activation in sepsis, stimulating the formation of anti-inflammatory lipoxin A₄ (20), with a protective effect against acute lung injury. Chen and coworkers found that critically ill patients taking aspirin had a significantly lower prevalence of adult respiratory distress syndrome (ARDS) (27% versus 34%; *P* = 0.034) (21). Chronic aspirin therapy has been also associated with improved survival rates for both patients with CAP (13) and those with sepsis (22).

The novelty of our study is that we found a synergistic effect of aspirin and macrolides. Our study suggests that aspirin and macrolides have different and complementary effects in patients with severe pneumonia. The prehospital use of aspirin combined with the initial in-hospital use of a macrolide may interfere with the overwhelming inflammatory response. Furthermore, as suggested by previous studies (1, 8, 23, 24), the antiplatelet activity of aspirin may reduce the occurrence of acute cardiovascular events secondary to pneumonia, with a beneficial effect on mortality rates. As a matter of fact, the mortality rate observed in the ASMG was lower than that observed in the other groups, despite those patients having a higher frequency of previous cardiovascular diseases; as shown in Fig. 3, differences in survival rates among the 4 study groups were substantially observed after the first 10 days of treatment. This finding may be due to the role of aspirin in improving survival rates for patients at highest risk of cardiovascular complications due to baseline chronic heart disease (25, 26).

However, it is important to consider that therapy with macrolides and aspirin also has some disadvantages. For example, the greater bacteremia observed in the aspirin group may result from blocking of the benefit of platelets on extracellular traps and

TABLE 2 Radiological features, laboratory findings, and outcomes for patients with severe pneumonia in the 4 study groups

Variable ^a	ASMG (n = 148)	ASG (n = 237)	MG (n = 294)	NASMG (n = 616)	P ^b
Radiological and laboratory findings					
Pleural effusion (no. [%])	56 (37.8)	112 (47.2)	121 (41.1)	244 (39.6)	0.06
Bilateral pneumonia (no. [%])	61 (41.2)	102 (43)	176 (59.8)	323 (52.4)	<0.001
Leukocytosis (leukocyte count of ≥10,000 leukocytes/μl) (no. [%])	67 (45.3)	143 (60.3)	177 (60.2)	371 (60.2)	0.10
Leukopenia (leukocyte count of <4,000 leukocytes/μl) (no. [%])	20 (13.5)	48 (20.2)	102 (34.7)	236 (38.3)	<0.001
Uremia (BUN level of ≥20 mg/dl) (no. [%])	61 (41.2)	126 (53.1)	171 (58.1)	303 (49.2)	0.77
Platelet count of <100,000 mm ³ (no. [%])	11 (7.4)	49 (20.6)	65 (22.1)	99 (16.1)	0.07
PaO ₂ /FiO ₂ ratio of <250 (no. [%])	74 (50)	127 (53.6)	174 (59.2)	356 (57.8)	0.15
MDR etiology (no. [%])	17 (11.4)	38 (16)	32 (10.9)	137 (22.2)	<0.001
Therapies					
Use of inotropic agents (no. [%])	55 (37.1)	56 (23.6)	57 (19.4)	178 (28.9)	<0.001
CRRT (no. [%])	10 (6.7)	21 (8.8)	24 (8.1)	50 (8.1)	0.82
ARDS (no. [%])	17 (11.4)	18 (7.6)	28 (9.5)	84 (13.6)	0.08
NIV use (no. [%])	32 (21.6)	25 (10.5)	48 (16.3)	86 (13.9)	0.006
Mechanical ventilation (no. [%])	20 (13.5)	55 (23.2)	50 (17)	96 (15.6)	0.03
Outcomes					
Cardiovascular events during hospitalization (no. [%])	37 (25)	55 (23.2)	45 (15.3)	104 (16.8)	0.007
Length of hospitalization (median [IQR]) (days)	11 (1–26)	15 (1–26)	12 (1–25)	15 (3–28)	<0.001
Length of therapy (median [IQR]) (days)	11 (1–13)	10 (1–15)	10 (3–13)	11 (4–14)	0.026
Admission to ICU (no. [%])	32 (21.6)	86 (36.3)	101 (34.3)	211 (34.2)	0.045
30-day death (no. [%])	23 (15.5)	50 (21.1)	70 (23.8)	174 (28.2)	0.005

^aIQR, interquartile range; CRRT, continuous renal replacement therapy; ARDS, acute respiratory distress syndrome; NIV, noninvasive ventilation; ASMG, aspirin plus macrolide group; ASG, aspirin-only group; MG, macrolide-only group; NASMG, no aspirin or macrolide group.

^bDescriptive P values for the nonparametric ANOVA/chi-square hypothesis that ≥1 group differs from the others.

other attempts to prevent bacteria from gaining access to the vascular space. This effect could be overcome in a randomized clinical trial by starting aspirin therapy after admission for CAP. Finally, clinicians should carefully weigh the potential cardiovascular adverse effects of macrolides, especially for patients with a high risk of arrhythmias (27).

Our study has some strengths and several limitations. The observational design of the study is an intrinsic limitation, because lack of randomization precludes definitive analysis of the benefit of aspirin plus macrolides, and the sample size planned in the protocol was not reached for the ASMG. We attempted to reduce the potential bias due to confounding variables that could be found in an estimate of the treatment effect obtained by simply comparing outcomes by using the propensity score matching technique. Moreover, the population analyzed was very old (the median age was

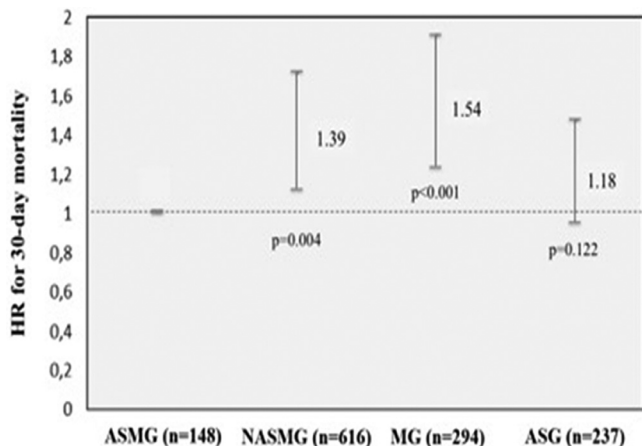


FIG 2 HRs for 30-day death among the 4 study groups after propensity score weighting. ASMG, aspirin plus macrolide group; ASG, aspirin-only group; MG, macrolide-only group; NASMG, no aspirin or macrolide group.

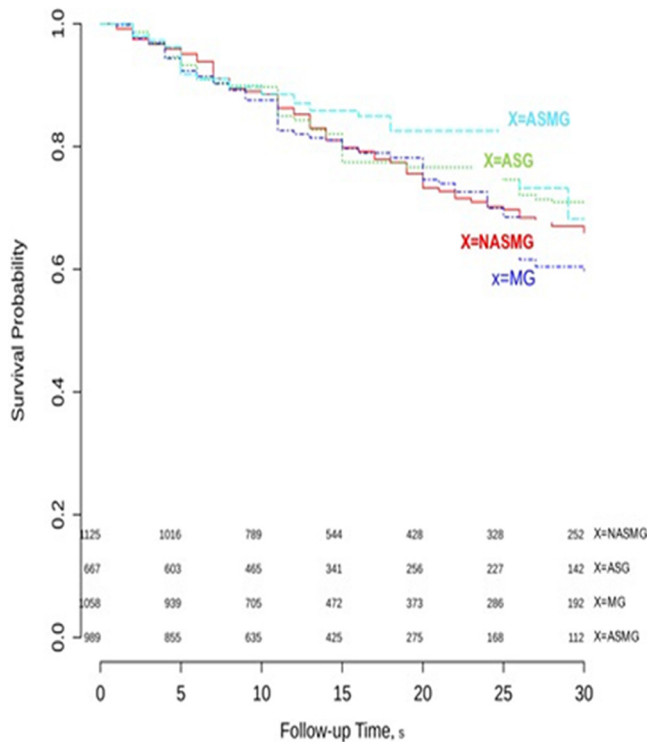


FIG 3 Kaplan-Meier curves of 30-day survival rates after propensity score analysis. ASMG, aspirin plus macrolide group; ASG, aspirin-only group; MG, macrolide-only group; NASMG, no aspirin or macrolide group.

77 years), and these data should not be extrapolated to all patients with community-onset pneumonia. As shown in Table 1, few patients who had septic shock or were treated with inotropic agents were admitted to ICUs, especially in the ASMG. The potential explanation for this finding could be that patients with septic shock died in the emergency department, before transfer to other wards. Finally, considering the possible role of aspirin in reducing cardiovascular events, a subanalysis of differences in aspirin dosages and effects on survival rates was not performed. Further studies, preferably randomized clinical trials, are needed to evaluate this potential mechanism.

The strength of the study is its international multicenter design and the analysis of severe pneumonia in real settings, which suggests that aspirin in combination with macrolides may have a positive impact on mortality rates independent of other confounding factors. Of importance, users of aspirin plus macrolides and nonusers of aspirin plus macrolides were well balanced in terms of demographic and clinical characteristics and had no differences in concomitant diseases, which could bias the results.

In conclusion, our study provides clinical evidence that the combination of aspirin plus a macrolide could improve survival rates for patients with severe CAP; the optimal management of severe CAP may consist of a multifaceted therapeutic approach with antimicrobial, anti-inflammatory, and antiplatelet agents. Considering the observational methodology of the study, randomized clinical trials are warranted to support this finding.

MATERIALS AND METHODS

Study design and patient selection. This observational study was conducted between 2011 and 2015 with patients enrolled in the following university hospitals: (i) Policlinico Umberto I, Sapienza University of Rome (Rome, Italy); (ii) Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine (St. Louis, MO, USA); (iii) Nagoya University Graduate School of Medicine (Nagoya, Japan); (iv) Zhejiang University School of Medicine (Hangzhou, China); and (v) Internal and Emergency Medicine Unit, Careggi General and University Hospital (Florence, Italy). The availability of

standard methods for diagnosis and the possibility to apply the same study design and to establish identical outcomes provided the rationale to pool patients' data. Patients who fulfilled the following criteria were enrolled in the study: (i) age of ≥ 18 years; (ii) clinical presentation of an acute illness with ≥ 2 of the following signs or symptoms suggesting pneumonia: rales, rhonchi, bronchial breath sounds, fever ($>38.0^{\circ}\text{C}$), tachycardia, chills, dyspnea, coughing (with or without sputum), and/or chest pain; (iii) presence of new consolidation(s) on chest X rays; and (iv) criteria for severe pneumonia (5). This analysis was reported according to the STROBE recommendations (28).

Only patients who were treated with aspirin before admission were included in the study, while patients who received aspirin during hospitalization were not recruited. Prehospital use of aspirin was defined according to the patients' pharmacological history. Patients who had an anamnestic or new intolerance/allergy to a macrolide or aspirin, had a rapidly progressive neoplasm, or had received a solid organ or hematopoietic stem cell transplant were excluded from the final analysis. Patients who had received macrolides prior to hospitalization were also excluded. Pneumonia was considered CAP if it was diagnosed upon hospitalization and the patient had not been discharged from an acute care facility within 14 days preceding the clinical presentation (29). The present study was conducted according to the principles stated in the Declaration of Helsinki. The local ethics committees of all participating hospitals approved the study.

Baseline assessment and definitions. Data on demographic characteristics, comorbidities, and antibiotic and concomitant therapy were collected. Baseline comorbidities were defined as described previously (30). Baseline treatments were defined according to the patients' pharmacological history. Stratification of the severity of pneumonia at presentation was performed using PSI and CURB-65 scores (31). In-hospital cardiovascular events, as defined previously (32), were recorded.

Diagnosis of severe pneumonia was based on the Infectious Diseases Society of America/American Thoracic Society consensus guidelines (5), i.e., 1 major criterion (invasive mechanical ventilation or septic shock with the need for vasopressors) or 3 minor criteria (respiratory rate of ≥ 30 breaths/min, partial pressure of arterial oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] ratio of ≤ 250 , multilobar infiltrates, confusion/disorientation, uremia [blood urea nitrogen [BUN] level of ≥ 20 mg/dl], leukopenia [white blood cell [WBC] count of $<4,000$ cells/ mm^3], thrombocytopenia [platelet count of $<100,000$ cells/ mm^3], hypothermia [core temperature of $<36^{\circ}\text{C}$], or hypotension requiring aggressive fluid resuscitation) (5). Sepsis and septic shock were defined according to the new definitions of 2016 (38). For patients who underwent an etiological diagnosis, microbiological examinations performed on blood and respiratory specimens during the first 24 h after admission, according to standards of practice, were evaluated for assessment of microbial etiology. The etiology was considered definite if 1 of the following criteria was met (17): positive blood culture in the absence of an apparent extrapulmonary focus; positive bacterial culture of pleural fluid; positive urinary antigen for *Legionella pneumophila*; positive urinary antigen for *Streptococcus pneumoniae*; bacterial yield in cultures of valid sputum (>25 polymorphonuclear cells and <10 epithelial cells per high-power field) of $\geq 10^6$ CFU/ml, of tracheobronchial aspirates of $\geq 10^5$ CFU/ml, of bronchoalveolar lavage fluid of $\geq 10^4$ CFU/ml, or of protected specimen brush cultures of $\geq 10^3$ CFU/ml; or occurrence of seroconversion (a 4-fold increase in IgG titers for *Chlamydia pneumoniae* [1:512] or an increase in IgM titers for *C. pneumoniae* [1:32] or *Mycoplasma pneumoniae* [any titer]). Diagnostic methods were similar for all study centers. Patients were considered to have MDR pathogens if one of the following was isolated: methicillin-resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas maltophilia*, or extended-spectrum β -lactamase (ESBL)-producing or carbapenem-resistant *Enterobacteriaceae*. For the remaining cases, MDR was defined as isolation of a bacterial strain that was nonsusceptible to ≥ 1 agent in ≥ 3 antimicrobial categories (33).

Study groups and endpoints. Four study groups were identified, i.e., (i) patients receiving aspirin plus macrolides (ASMG), (ii) patients receiving aspirin alone (ASG), (iii) patients receiving a macrolide alone (MG), and (iv) patients receiving neither aspirin or macrolides (NASMG). We considered patients taking aspirin if their daily intake was ≥ 100 mg. Compliance with therapy was assessed by collection of medical history at the time of hospitalization. All patients were considered receiving macrolide treatment if they received ≥ 48 h of therapy with 500 mg of clarithromycin every 12 h or 500 mg of azithromycin every 24 h. The primary endpoint was the evaluation of 30-day survival rates for patients with severe pneumonia treated with aspirin plus macrolides, compared to the other groups.

Sample size. The primary endpoint concerned the supremacy of the combination therapy (ASMG), with respect to the other groups, in increasing the 30-day survival rate. We tested the union null hypothesis that the combination therapy was equivalent to each of the other 3 groups. Consequently, a union-intersection test was built, and its P value was the one corresponding to the largest of the 3 P values computed. Assuming a survival rate of 85% for the ASMG, a survival rate of 75% for the ASG, and lower survival rates for the other 2 groups, a sample size of ≥ 247 patients per group was calculated to guarantee a power of $\geq 80\%$ to detect a significant difference, with a significance level of 5%.

Statistical analysis. Data were collected through an electronic database. The results obtained were analyzed using commercially available statistical software packages (SPSS v20.0 [SPSS Inc., Chicago, IL] and R v3.3.3 [R Development Core Team]).

To detect significant differences between groups, we used the chi-square test or the Fisher exact test for categorical variables and the 2-tailed t test or the Mann-Whitney test for continuous variables, as appropriate. Comparisons among ≥ 3 groups were performed with univariate analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. *Post hoc* tests were adjusted for multiplicity through Bonferroni correction. We report adjusted significance levels, which can be interpreted as usual P values.

Survival curves for time-to-event variables were constructed with the use of Kaplan–Meier estimates based on all available data and were compared with the use of the log-rank test. In a multivariate analysis

of survival times, the Cox regression model was used to determine the effects of different variables on overall survival rates. Wald CIs and tests for odds ratios were computed based on the estimated standard errors.

Finally, to correct for possible bias arising from the observational nature of the experiment, we weighted all relevant effect estimates and *P* values by propensity score analysis (34), using relevant prehospitalization variables and factors measured at the time of hospital admission. We determined the candidate variables *a priori*, referring to reported risk factors for death in previous studies (3, 5, 10, 18, 35, 36, 37). The variables included age, sex, CURB-65 class III, presence of ≥ 2 comorbidities, cardiovascular disease, liver disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), renal disease, neoplasm, previous hospitalization, pleural effusion, delirium, PaO₂/FIO₂ ratio of <250, ARDS, bacteremia, leukopenia, MDR etiology, septic shock, and ICU admission (a full description is provided in Table S3 at <https://www.alariconetwork.com/novita-scientifiche>). The propensity score for the 4 treatment levels was estimated using boosted logistic regression, by minimizing the maximal standardized difference between each pair of treatment levels for each pretreatment variable.

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