EFFECTIVENESS OF COMBINATION THERAPY VERSUS MONOTHERAPY WITH A THIRD-GENERATION CEPHALOSPORIN IN BACTEREMIC PNEUMOCOCCAL PNEUMONIA. A PROPENSITY SCORE ANALYSIS.

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Keywords: Pneumococcal pneumonia; bacteremia; combination therapy; mortality; propensity score

Running title: Combined treatment in pneumococcal pneumonia

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Abstract

Objective: combining a macrolide or a fluoroquinolone to beta-lactam regimens in the treatment of patients with moderate to severe community-acquired pneumonia is recommended by the international guidelines. However, the information in patients with bacteremic pneumococcal pneumonia is limited.

Methods: a propensity score technique was used to analyse prospectively collected data from all patients with bacteremic pneumococcal pneumonia admitted from 2000 to 2015 in our institution, who had received empirical treatment with third generation cephalosporin in monotherapy or plus macrolide or fluoroquinolone.

Results: we included 69 patients in the monotherapy group and 314 in the combination group. After adjustment by PS for receiving monotherapy, 30-day mortality (OR 2.89; 95% CI 1.07 – 7.84) was significantly higher in monotherapy group. A higher 30-day mortality was observed in monotherapy group in both 1:1 and 1:2 matched samples although it was statistically significant only in 1:2 sample (OR (CI95%): 3.50 (1.03 - 11.96), *P*=0.046).

Conclusions: our study suggests that in bacteremic pneumococcal pneumonia, empirical therapy with a third-generation cephalosporin plus a macrolide or a fluoroquinolone is associated with a lower mortality rate than beta-lactams in monotherapy. These results support the recommendation of combination therapy in patients requiring admission with moderate to severe disease.

Introduction

Community-acquired pneumonia (CAP) remains a frequent cause of hospitalization with a significant morbidity and mortality, and accounts for a high burden of health care costs (1). Optimal coverage of *Streptococcus pneumoniae* is recommended particularly for patients that required hospitalization. British Thoracic Society (BTS), Infectious Diseases Society of America/ American Thoracic Society (IDSA/ATS) and European guidelines recommend combined treatment with a beta-lactam plus a macrolide for CAP requiring hospital admission (2, 3). The beneficial effect of combined therapy was reviewed in a meta-analysis published in 2014 (4), and authors concluded that from observational studies the addition of a macrolide might reduce the mortality risk of patients with CAP. Nevertheless, a recent cluster-randomized, crossover trial with strategies rotated in 4-month periods (beta-lactam, beta-lactam plus macrolide or fluoroquinolone), concluded that beta-lactam monotherapy for CAP requiring hospital admission was not inferior to other strategies regarding 90-day mortality (5). Therefore, the debate about the need for combined treatment in patients with CAP is still open, particularly for those with moderate to severe CAP. *S. pneumoniae* is the most frequently isolated pathogen in CAP and although the mortality of pneumococcal pneumonia is low, it increases in the presence of bacteremia or in patients with major comorbidities (6, 7). There are few data about the benefit of combined therapy in bacteremic pneumococcal pneumonia (8) and the majority of the studies evaluated the combination of macrolides with beta-lactams (9-10) but the experience with fluoroquinolones combined with beta-lactams is scarce (11).

The objective of our study was to assess the 30-day mortality of patients with bacteremic pneumococcal pneumonia receiving empirical treatment with a combination including a third-generation cephalosporin and a macrolide or a fluoroquinolone and to compare both with patients receiving a third-generation cephalosporin in monotherapy. A retrospective analysis of data collected over 15 years of all consecutive episodes of

pneumococcal bacteremic pneumonia admitted in our centre was performed and a propensity analysis was applied to minimize the treatment selection bias.

Patients and methods

The study was conducted in a 700-bed university hospital in Barcelona, Spain. From January 2000 to December 2015, an infectious disease specialist prospectively collected clinical and microbiological data from all patients with community bacteremic pneumococcal pneumonia. The following variables were gathered: age, sex, prognosis of the underlying disease, comorbidities, antibiotic or steroids treatment in the previous month, presence of fluid refractory hypotension and intensive care unit admission and empirical and definitive antibiotic treatment. The patients were followed during the 30 days after the admission or until his death. We selected for the study those patients who had received empirical treatment with a third generation cephalosporin in monotherapy or in combination with a macrolide or a fluoroquinolone.

Definition of terms. Bacteremic pneumococcal pneumonia was defined as positive blood culture for *S. pneumoniae* for a patient with respiratory symptoms and a new pulmonary infiltrate documented by chest radiography. The isolation of *S. pneumoniae* in a respiratory sample was not mandatory to diagnosis. Underlying diseases were classified according to the McCabe and Jackson modified criteria into rapidly fatal, finally fatal, or non-fatal (12). Previous treatment with steroids was defined if patient had taken at least a dose of 10 mg of prednisone or equivalent during the previous month to admission. Fluid refractory hypotension within the 24 hours of diagnosis was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Appropriate empirical therapy was considered when the patient received active monotherapy (with a third generation cephalosporin) or combined therapy (with a third generation cephalosporin plus a macrolide or a fluoroquinolone) within 24 h after

obtaining blood cultures, before susceptibility results were available. Resistance to penicillin or macrolide was defined according to EUCAST criteria (MIC > 2 mg/L for penicillin and > 0.5 mg/L for erythromycin).

Microbiological procedures. Blood samples were processed using the BD BACTEC 9240 and BD BACTEC FX systems (Becton Dickinson, Franklin Lakes, NJ), with an incubation period of 5 days. Isolates were identified by standard techniques. Minimal inhibitory concentrations (MICs) were determined by broth microdilution (Sensititre, Trek Diagnostic Systems, West Sussex, UK). EUCAST guidelines were used for interpretation of MICs results.

Statistical analysis. The whole study sample was divided into two groups: patients who received empirical therapy with a third-generation cephalosporin plus a macrolide or a fluoroquinolone (combination group) and patients who received monotherapy with a third-generation cephalosporin (monotherapy group). First, a descriptive analysis of the whole sample and a comparative analysis between groups were performed. Continuous variables are expressed as mean (standard deviation), and compared using the Student's t-test, while categorical variables are expressed as absolute frequency (percentage), and compared using the χ^2 test, or the Fisher's exact test when necessary. Second, due to the absence random allocation to treatment groups, derived from the observational nature of our study, we used a propensity score (PS) method to minimize differences between both groups (13). To do so, we used a non-parsimonious logistic regression model including empirical monotherapy with cephalosporin as dependent variable and other variables potentially associated with the decision to initiate empirical monotherapy as covariates. The latter variables included only baseline factors. Accordingly, the covariates introduced in logistic regression model to estimate the PS were: age ≥ 65 years, sex, comorbid conditions, non-fatal prognosis (according to McCabe and Jackson index), previous treatment with steroids, neutropenia and septic shock at diagnosis. Once this model was obtained, the PS was used to evaluate the association between cephalosporin monotherapy, as

empirical treatment, with 7-day and 30-day mortality by propensity-matched analysis (14). Propensity-matched analysis was performed by matching patients of both groups at 1:1 and 1:2 ratio, without replacement, by the nearest neighbor technique. A caliper of width equal to 0.2 of the pooled standard deviation of the logit of PS was the criterion used for matching pairs (15). The standardized difference was further used to assess whether matching technique properly balanced the characteristics of groups (16). Absolute values of standardized difference < 10% supported the assumption of balance between groups (17). After matching, PS was included in multivariate conditional logistic regression models to assess their potential effects on the association between empirical treatment and 7-days and 30-days mortality. The estimated PS was also used in the whole sample as a covariate in multivariate logistic regression analysis of 7-days and 30-days mortality (18). A *P* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 20 for Mac (SPSS Inc, Chicago, Illinois, United States) and a PS matching custom dialog for SPSS (Thoemmes F.; Cornell University; http://arxiv.org/pdf/1201.6385v1.pdf; Accesed 23 February 2016) (19).

Results

Baseline characteristics of patients.

From 2000 to 2015, 681 patients with pneumococcal bacteremic pneumonia were admitted in our institution. Of these, 383 (56.2%) had received monotherapy with a third generation cephalosporin or combined therapy with a macrolide or a fluoroquinolone within 24 h after obtaining blood cultures, therefore were eligible for the study (Figure 1). Mean age was 60.8 (SD: 18.9) and 234 (61.1%) were males. The main comorbidities were chronic obstructive pulmonary disease (COPD) (21.4%), HIV infection (18.3%) and diabetes mellitus (15.9%). Eighty-eight patients (23.0%) had a finally o rapidly-fatal prognosis of their basal comorbidities. Treatment with

corticosteroids was present in 28 patients (7.3%). Fluid refractory hypotension at admission was diagnosed in 12.5 % and 30-days mortality was 5.0% of the whole sample. Penicillin resistance and macrolide resistance was present in 9.2% and 15.8% of *S. pneumoniae* strains, respectively, remaining stable during the study period. Only one of the *S. pneumoniae* strains had a MIC of cefotaxime >2 mg/L, and 27 (7.3%) showed an intermediate susceptibility to cefotaxime (MICs between 1 to 2 mg/L).

Characteristics of treatment groups.

Of the included patients, 69 (18.0%) empirically received a third generation cephalosporin in monotherapy, and 314 (82.0%) as a part of a combined therapy with a macrolide or a fluoroquinolone. Ceftriaxone was the cephalosporin used in 97.6 % of cases. Among patients receiving macrolides, in 161 (87.9 %) it was azithromycin, 19 (10.4%) clarithromycin and 3 patients received erythromycin. The most used fluoroquinolone was levofloxacin, in 98.5 % of patients.

Comparative characteristics of both groups are shown in table 1. Patients in the monotherapy group were older and had a worse prognosis of their underlying disease according to McCabe and Jackson criteria, although these differences were not statistically significant. A significantly higher prevalence of chronic hepatic disease was observed in monotherapy group (14.5 % vs 5.4 %, P= 0.008). Other comorbidities such as COPD, HIV infection, haematologic or solid neoplasm were similar between groups. Septic shock at diagnosis was present in 8.7% of patients in the monotherapy group and in 13.4% of those in the combined group.

Within the combined treatment group, there were no differences between those receiving a macrolide or a fluoroquinolone in the main baseline comorbidities, except for increased cardiovascular and haematological neoplasm in patients receiving a fluoroquinolone (data not shown). Although the presence of fluid refractory hypotension was more frequent in the fluoroquinolone group than in the macrolide group (19.1% vs.

9.3%, P=0.012), there were no differences in 30-days mortality. Accordingly, both were grouped.

Influence of empirical treatment on mortality.

A total of 19 patients (5%) died within 30 days of admission. Variables associated with mortality in the univariate analysis (table 2) were age ≥ 65 years, the presence of chronic liver disease or cardiovascular disease, a finally or rapidly-fatal prognosis of basal comorbidities, fluid refractory hypotension at admission and to receive empirical monotherapy with a cephalosporin. Among patients who died within 30 days of bacteremia, 57.9% had received combined therapy compared to 83.2% of those who did not die (P = 0.005). Results were similar when 7-days mortality was the endpoint (data not shown).

In order to control for a selection bias, a PS analysis was performed and patients were matched accordingly. The groups were homogenously balanced both in 1:1 and 1:2 matched samples and standardized differences were < 10% (table 3). In 1:1 matched sample, the 7-days mortality rate was 7.7% for patients who received third generation cephalosporin monotherapy and 1.5% for patients who received combined therapy (standardized difference 13.9%), whereas the 30-days mortality rate was 10.8% and 1.5%, respectively (standardized difference 19.8%). In 1:2 matched sample both 7-days (7.7% vs. 2.3%; standardized difference 11.7%) and 30-days mortality rate (10.8% vs. 3.9%; standardized difference 13.7%) were higher in patients receiving third generation cephalosporin monotherapy (table 3). Table 4 shows the 7-days and 30-days odds of mortality in matched samples. The 30-days odd of mortality was multiplied by 3.5 (95% CI 1.03-11.96) in the monotherapy group.

After adjustment by PS in the whole sample, 7-days mortality (OR 3.23; 95% CI 1.03 – 10.11) and 30-days mortality (OR 2.89; 95% CI 1.07 – 7.84) remained significantly higher in the monotherapy group than in combined group (table 5).

Discussion

In the present study, we have prospectively evaluated a large number of patients with bacteremic pneumococcal pneumonia, and after an accurate analysis using a propensity score technique, our results suggests that combination treatment including a third-generation cephalosporin plus a macrolide or a fluoroquinolone decreases the mortality rate in comparison to beta-lactam monotherapy. Indeed, after adjusting for possible confounding factors, patients receiving in the first 24 hours a combined therapy had about 3 times higher probability to survive within 30 days than those receiving monotherapy. Our results support previous studies with similar conclusions (9, 20, 21) but our approach has several strengths that are critical to understand the value of combined therapy for pneumococcal disease. Firstly, all patients had bacteremia and required hospital admission for ≥48h, therefore, all had at least a moderate to severe infection. The controversial about the beneficial effect of combined therapy in pneumococcal pneumonia could be related with the severity of cases analyzed in each study. A recently published trial (5) showed a non-inferiority of beta-lactam monotherapy vs. combination therapy in adults with CAP but patients had a mild disease (median CURB-65 score of 1) and the fact that intensive care admission was an exclusion criterion. In contrast, a previous trial described a trend towards a superiority of the combined therapy among patients with a severe illness (22) and a large observational study including 5240 hospitalised adults with CAP from England and Wales observed a lower mortality rate by using beta-lactam plus macrolide combination only among patients with a CURB-65 score ≥2 but not for those with a CURB-65 ≤1 (23). Secondly, only patients receiving a third-generation cephalosporin (ceftriaxone in >95%) were included, avoiding the inclusion of different beta-lactams with lower activity against *S. pneumoniae* (e.g. cefuroxim) (24). Thirdly, combined therapy included only macrolides (88% azithromycin) or fluoroquinolones (97% levofloxacin) while previous studies included any other antibiotic (25).

On the other hand, we also analyzed the characteristics of patients receiving combination therapy with a macrolide or a fluoroquinolone and no difference in terms of mortality was observed between these 2 groups of patients. This is in contrast to a previous study that found a significantly higher mortality rate among patients receiving a beta-lactam plus a fluoroquinolone than in any other regimen (26). The 30-day mortality was 30% (4 of 13) for patients who received a beta-lactam with a fluoroquinolone, compared with 7.4% (2 of 27) for other antibiotic regimes in pneumonia severity index classes I to III, 29% (4 of 14) compared with 12% (4 of 34) in class IV, and 30% (7 of 23) compared with 21% (13 of 61) in class V. Although the authors included a propensity score, the low number of cases and a mortality rate in the fluoroquinolone group of 30% even in PSI classes I-III suggests that these patients had particular characteristics not capture by their analysis. In agreement with our results, a recently published meta-analysis (27), with over 16.000 patients included, did not find statistically significant differences in the mortality rate of patients receiving a beta-lactam plus a macrolide or a fluoroquinolone. Fourthly, this is the first observational study in bacteremic pneumococcal pneumonia that includes a propensity score analysis and a matching 1:1 and 1:2 to reduce biases related to empirical treatment selection. Differences in age, underlying diseases, and severity of infection were used to develop a propensity score for combination therapy vs. monotherapy. The characteristics of both groups after matching were comparable except in 7 and 30-day mortality rate.

The beneficial effect of the association with a macrolide or a fluoroquinolone could be attributed to 1) a broad-spectrum coverage including atypical pathogens and resistant to third-generation cephalosporins *S. pneumoniae*. However, it is difficult to assume this effect plays any role particularly in our study where all patients had *S. pneumoniae* bacteremia, and the prevalence of cephalosporin resistance is very low, 2) synergism against pneumococci that has been observed between third-generation cephalosporins

and levofloxacin in 54% of the strains tested in one study (28) but not for macrolides (29, 30), therefore, it seems unlikely that synergism was the beneficial effect of combination, 3) anti-inflammatory effect that has been described for macrolides and fluoroquinolones mediated in both cases by the inhibition of NF-kß transcription factor that leads to a reduction in the production of pro-inflammatory cytokines (31-33) and subsequent beneficial immunomodulatory effects (34, 35), and 4) virulence reduction of *S. pneumoniae* by inhibiting the production of pneumolysin that has been demonstrated with macrolides and fluoroquinolones and it is independent of the strain susceptibility (36-38). Pneumolysin facilitates intraalveolar replication of pneumococci, penetration of bacteria from alveoli into the interstitium of the lung, and dissemination of pneumococci into the bloodstream during experimental pneumonia (39). Indeed, the inhibition of virulence factors production has demonstrated a clinical benefit also in other entities such as *Streptococcus pyogenes* necrotizing fasciitis. Although clindamycin and penicillin are antagonistic *in vitro*, combination improves the outcome of these patients (40).

Our study has several limitations; firstly, it was a retrospective observational study, although the data were collected during the active follow-up of the patient by a specialist in infectious diseases from the time of admission and during the subsequent 30 days. Secondly, sputum for culture was not obtained in all patients, therefore, we cannot ensure the presence of other microorganisms, however; the prevalence of polymicrobial infection is low (41). Thirdly, severity scores (PSI, CURB-65) were not prospectively collected and this could be a major limitation since correction for mortality risk groups was not performed. However data about age, comorbidity, and the presence of fluid refractory hypotension were gathered allowing us to perform an accurate matching by propensity score technique.

In conclusion, our study suggests that empirically administration of combined therapy is associated with a lower mortality rate than beta-lactam in monotherapy in patients with

bacteremic pneumococcal pneumonia, and no difference between patients receiving a macrolide or a fluoroquinolone was observed. These results support the recommendation of combination therapy for the treatment of pneumococcal pneumonia in patients requiring admission with moderate to severe disease and suggest that the beneficial effect could be related to the anti-inflammatory effect and the capacity to reduce *S. pneumoniae* virulence exhibited by both macrolides and fluoroquinolones. This is a retrospective study with some limitations, and in the future, it is necessary to confirm our results by designing clinical trials that capture the patients that potentially could benefit from combination therapy.

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Table 1. Characteristics of patients according to the empirical treatment received.

Variables	Monotherapy (n= 69)	Combination therapy (n= 314)	*P*
Age ≥ 65 years, n (%)	39 (56.5)	137 (43.8)	0.054
Male sex, n (%)	38 (55.1)	196 (62.4)	0.257
Without comorbidities, n (%)	17 (24.6)	92 (29.3)	0.437
Non-fatal prognosis[1], n (%)	47 (68.1)	248 (79.0)	0.052
Chronic liver disease, n (%)	10 (14.5)	17 (5.4)	0.008
Diabetes mellitus, n (%)	10 (14.5)	51 (16.2)	0.719
Chronic obstructive pulmonary disease, n (%)	12 (17.4)	70 (22.3)	0.369
Kidney chronic disease, n (%)	2 (2.9)	14 (4.5)	0.747
Chronic alcohol intake	2 (2.9)	12 (3.8)	>0.999
Cardiovascular disease, n (%)	10 (14.5)	27 (8.6)	0.133
HIV infection, n (%)	14 (20.3)	56 (17.8)	0.633
Haematologic neoplasia, n (%)	6 (8.7)	31 (9.9)	0.764
Solid neoplasm, n (%)	4 (5.8)	13 (4.1)	0.522
Neutropenia, n (%)	0	2 (0.6)	>0.999
Splenectomy, n (%)	1 (1.4)	3 (1)	0.550
Corticosteroid treatment, n (%)	6 (8.7)	22 (7)	0.625
Penicillin resistance[2], n (%)	3 (4.3)	32 (10.3)	0.166
Erythromycin resistance[3], n (%)	14 (20.3)	46 (14.8)	0.257
Fluid refractory hypotension, n (%)	6 (8.7)	42 (13.4)	0.288
30-days mortality, n (%)	8 (11.6)	11 (3.5)	0.005
7- days mortality, n (%)	6 (8.7)	8 (2.5)	0.014

[1] according to McCabe and Jackson criteria (see patients and methods)

[2] this information was available in 381 patients

[3] this information was available in 380 patients

Table 2. Association between characteristics of patients and 30-day mortality.

Variables	Alive n= 364 (95)	Dead n= 19 (5)	*P*
Age ≥ 65 years, n (%)	161 (44.4)	15 (78.9)	0.004
Male sex, n (%)	226 (62.1)	8 (42.1)	0.082
Non-fatal prognosis[1], n (%)	284 (78.0)	11 (57.9)	0.042
Without comorbidities, n (%)	106 (29.1)	3 (15.8)	0.298
Chronic liver disease, n (%)	21 (5.8)	6 (31.6)	<0.001
Diabetes mellitus, n (%)	58 (15.9)	3 (15.8)	>0.999
Chronic obstructive pulmonary disease, n (%)	77 (21.2)	5 (26.3)	0.593
Kidney chronic disease, n (%)	16 (4.4)	0	>0.999
Chronic alcohol intake	11 (3.0)	3 (15.8)	0.027
Cardiovascular disease, n (%)	31 (8.5)	6 (31.6)	0.001
Intravenous drug abuser, n (%)	2 (0.5)	0	>0.999
HIV infection, n (%)	70 (19.2)	0	0.031
Haematologic neoplasia, n (%)	36 (9.9)	1 (5.3)	>0.999
Solid neoplasm, n (%)	16 (4.4)	1 (5.3)	0.587
Splenectomy, n (%)	3 (0.8)	1 (5.3)	0.185
Neutropenia, n (%)	2 (0.5)	0	>0.999
Corticosteroid treatment, n (%)	27 (7.4)	1 (5.3)	>0.999
Penicillin resistance[2], n (%)	33 (9.1)	2 (10.5)	0.690
Erythromycin resistance[3], n (%)	57 (15.8)	3 (15.8)	>0.999
Fluid refractory hypotension, n (%)	35 (9.6)	13 (68.4)	<0.001
Combined treatment, n (%)	303 (83.2)	11 (57.9)	0.005

[1] according to McCabe and Jackson criteria (see patients and methods)

[2] this information was available in 381 patients

[3] this information was available in 380 patients

Table 3. Main characteristics of patients with bacteremic pneumococcal pneumonia according to empirical treatment received after matching by propensity score.

Variables	Matched 1:1 sample			Matched 1:2 sample		
	Empirical treatment, n (%)		SD[1]	Empirical treatment, n (%)		SD[1]
	Monotherapy (N=65)	Combined therapy (N=65)		Monotherapy (N=65)	Combined therapy (N=129)	
Male sex	36 (55,4)	36 (55,4)	0,0	36 (55,4)	75 (58,1)	3,9
Age ≥65 years	35 (53,8)	35 (53,8)	0,0	35 (53,8)	77 (59,7)	8,3
Cardiovascular disease	9 (13,8)	9 (13,8)	0,0	9 (13,8)	23 (17,8)	6,6
Chronic obstructive pulmonary disease	12 (18,5)	13 (20,0)	2,4	12 (18,5)	27 (20,9)	3,9
Diabetes mellitus	10 (15,4)	9 (13,8)	2,6	10 (15,4)	23 (17,8)	4,0
Chronic kidney disease	2 (3,1)	1 (1,5)	4,0	2 (3,1)	3 (2,3)	1,9
Solid neoplasm	3 (4,6)	2 (3,1)	3,5	3 (4,6)	11 (8,5)	7,9
Hematologic neoplasia	6 (9,2)	4 (6,2)	6,0	6 (9,2)	10 (7,8)	2,8
Chronic liver disease	7 (10,8)	8 (12,3)	2,7	7 (10,8)	8 (6,2)	8,7
HIV infection	14 (21,5)	10 (15,4)	9,9	14 (21,5)	22 (17,1)	7,1
Chronic alcohol intake	2 (3,1)	3 (4,6)	3,5	2 (3,1)	4 (3,1)	0,1
Splenectomy	1 (1,5)	0 (0)	6,2	1 (1,5)	1 (0,8)	2,3
Intravenous drug abuser	0 (0)	0 (0)		0 (0)	0 (0)	
Non-fatal prognosis	47 (72,3)	50 (76,9)	7,0	47 (72,3)	95 (73,6)	2,0
Neutropenia	0 (0)	0 (0)		0 (0)	0 (0)	
Corticosteroid treatment	4 (6,2)	5 (7,7)	3,0	4 (6,2)	9 (7)	1,6
Fluid refractory hypotension	6 (9,2)	7 (10,8)	2,8	6 (9,2)	10 (7,8)	2,8
7-days mortality	5 (7,7)	1 (1,5)	13,9	5 (7,7)	3 (2,3)	11,7
30-days mortality	7 (10,8)	1 (1,5)	19,8	7 (10,8)	5 (3,9)	13,7

[1] Standardized difference

Table 4. Relationship between empirical monotherapy, combination therapy[1] and mortality matched by propensity score.

	OR (95% CI)[2]	*P* Wald[2]
1:1 Matched sample		
7-day mortality	5.00 (0.58 - 42.80)	0.142
30-day mortality	7.00 (0.86 - 56.90)	0.069
1:2 Matched sample		
7-day mortality	3.33 (0.80 - 13.95)	0.099
30-day mortality	3.50 (1.03 - 11.96)	0.046

[1] Combination therapy as reference and monotherapy as intervention.

[2] Data were obtained by conditional logistic regression analysis.

Table 5. Relationship between empirical monotherapy or combination therapy[1] and mortality considering the whole cohort.

	OR (95% CI)[2]	*P* Wald[2]
7-day mortality		
Unadjusted	3.64 (1.22 - 10.86)	0.02
Adjusted by PS	3.23 (1.03 - 10.11)	0.04
30-day mortality		
Unadjusted	3.61 (1.40 - 9.35)	0.008
Adjusted by PS	2.89 (1.07 - 7.84)	0.04

[1] Combined treatment as reference and monotherapy as intervention.

[2] Data were obtained by logistic regression analysis.

PS= propensity score.