

Predictive model for mortality in adults hospitalized for community-acquired pneumonia

Modelo predictivo para mortalidad en adultos hospitalizados con neumonía adquirida en la comunidad

Renata Báez-Saldaña^{1,2*}, Carlos Gómez-Zamora^{1,2}, Leticia Ferreyra-Reyes³, Norma Mongua-Rodríguez³, and Lourdes García-García³

¹Oncological Pulmonology Clinical Service, Instituto Nacional de Enfermedades Respiratorias, Mexico City; ²Postgraduate Division, Faculty of Medicine, Universidad Nacional Autónoma de México, Mexico City; ³Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico

Abstract

Introduction: There is lack of information about predictive variables for pneumonia mortality in the Mexican population.

Objective: The objective of the study was to identify a model for predictive variables for mortality in adults hospitalized with community acquired pneumonia (CAP).

Material and methods: Case-control study of patients hospitalized with CAP. The cases were incident cases with CAP that died during hospitalization and controls were those that did not die. The patients were followed during the study time until the discharge or outcome of each patient. The association between the independent variables (clinical, severity indices for pneumonia) with the outcome variable (in-hospital mortality) was evaluated by logistic regression. **Results:** The model of associated variables with mortality were: stratified age from 50-70 years (odds ratio [OR] 2.35; 95% confidence interval [95% CI]: 1.06-5.17) and age >70 years (OR: 2.75; 95% CI: 1.18-6.37), woman (OR: 2.05; 95% CI: 1.11-3.8), antecedent of arterial hypertension (OR: 0.40; 95% CI: 0.20-0.80), tachycardia (OR: 2.68; 95% CI: 1.16-6.17), tachypnea (OR: 2.85; 95% CI: 1.54-5.29), leukocytes $\geq 12,000$ (OR: 2.17; 95% CI: 1.21-3.87), and urea nitrogen > 30 mg/dL (OR: 4.85; 95% CI: 2.55-9.24).

Conclusions: The proposed risk model is easy to document with clinical history and routine clinical laboratory variables.

Keywords: Adults. Risk factors. Mortality. Community acquired pneumonia.

Resumen

Antecedentes: Existe escasa información sobre variables predictoras para mortalidad por neumonía en población mexicana.

Objetivo: Identificar un modelo de variables predictoras para mortalidad en adultos hospitalizados por neumonía adquirida en la comunidad (NAC).

Método: Estudio de casos y controles de pacientes hospitalizados por NAC. Los casos fueron pacientes con NAC que fallecieron durante la hospitalización y los controles fueron pacientes que no fallecieron. Los pacientes se siguieron durante el tiempo de estudio hasta el egreso o el desenlace de cada uno. La asociación entre las variables independientes (clínicas, índices de gravedad para neumonía) con la variable desenlace (muerte hospitalaria) se evaluó mediante regresión logística. **Resultados:** Las variables asociadas a mortalidad fueron la edad estratificada de 50-70 años (odds ratio [OR] 2.35; intervalo de confianza del 95% [IC 95%]: 1.06-5.17) y > 70 años (OR 2.75; IC 95%: 1.18-6.37), ser

Correspondence:

*Renata Báez-Saldaña

Tlalpan, 4502

Col. Sección XVI

C.P. 14080, Ciudad de México, México

E-mail: baezrd@unam.mx

Date of reception: 27-07-2019

Date of acceptance: 18-05-2020

DOI: 10.24875/CIRUE.M22000171

Cir Cir (Eng). 2020;88(5):571-577

Contents available at PubMed

www.cirugiaycirujanos.com

2444-0507/© 2020 Academia Mexicana de Cirugía. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

mujer (OR 2.05; IC 95%: 1.11-3.8), antecedente de hipertensión arterial (OR 0.40; IC 95%: 0.20-0.80), taquicardia (OR 2.68; IC 95%: 1.16-6.17), taquipnea (OR 2.85; IC 95%: 1.54-5.29), leucocitos $\geq 12,000$ (OR 2.17; IC 95%: 1.21-3.87) y nitrógeno de la urea >30 mg/dl (OR 4.85; IC 95%: 2.55-9.24). **Conclusiones:** El modelo de riesgo que se propone es fácil de documentar con la historia clínica y las pruebas de laboratorio habituales.

Palabras clave: Adultos. Factores de riesgo. Mortalidad. Neumonía adquirida en la comunidad.

Introduction

Community-acquired pneumonia (CAP) is a common and potentially serious disease. Although pneumonia mortality rate has declined since the introduction of antibiotic treatment in the 1940s, it is still regarded as one of the leading causes of morbidity and mortality worldwide.

In Mexico, in 2014, it was ranked as the 19th cause of morbidity, with 174,748 cases and a rate of 1.5 per 100,000 population; furthermore, in 2013 it was the 12th cause of mortality, with 17,417 cases, which corresponded to 2.8% of all-cause mortality in the country¹. At the National Institute of Respiratory Diseases (Instituto Nacional de Enfermedades Respiratorias [INER]), it is the second cause of emergency unit care and the first cause of hospital morbidity (data obtained from INER Medical Directorate, 2013-2017).

Severity evaluation is essential, since early identification of individuals at high risk of death can help deciding the site of medical care and a treatment plan. Therefore, CAP clinical guidelines start the treatment algorithm with severity evaluation by means of prediction rules for patient risk stratification²⁻⁴. The best validated and most commonly used risk prediction models are the CURB-65 scale⁵ (confusion, urea nitrogen ≥ 20 mg/dL, respiratory rate ≥ 30 breaths per min [bpm], systolic pressure < 90 mmHg or diastolic pressure ≤ 60 mmHg, and age older than 65 years) and the pneumonia severity index (PSI)⁶. These statistical predictive models were developed based on the identification of variables associated with mortality and allow to identify patients at low risk who can be treated on an outpatient basis and thereby reduce the costs of care. The previous studies have demonstrated their efficacy and safety for reducing hospitalization in patients at low risk for mortality; however, the proportion of hospitalized patients classified in this stratum ranges from 31% to 62.5%^{7,8}.

In Mexican patients, the risk factors associated with pneumonia mortality have been poorly explored, and their recognition is essential for an appropriate treatment according to the case, as well as for hospitalization decision. In this context, the purpose of the

present study was to identify and evaluate a model of variables predictive of mortality in adult patients hospitalized with CAP, and to measure the proportion of those classified as at low risk of mortality according to the PSI and CURB-65 indices.

Methods

The study protocol was approved by the institutional Research Ethics Committee. The results were handled in such a way that protection of individual rights and confidentiality was ensured.

Design, patients, setting, and period of study

Case-control study of consecutive hospitalized patients diagnosed with CAP, carried out from 2006 to 2013 in a reference hospital for respiratory diseases in Mexico City.

The study included hospitalized cases with a CAP diagnosis, defined as acute disease in which the patient has a new lung opacity associated with at least one of the following signs or symptoms: recent-onset cough, fever or hypothermia, leukocytosis or leukocytopenia, left shift, for which there is no other explanation and the disease is the main cause of hospital admission and will be treated as pneumonia⁹. Patients with post-obstructive pneumonia, history of hospitalization within 2 weeks before admission, nosocomial pneumonia, influenza-related pneumonia and any type of immunosuppression (either congenital or acquired), or under any immunosuppressive treatment were excluded from the study.

Case definition

Patient with CAP as admission diagnosis who died during hospitalization.

Control definition

Hospitalized patient with CAP as admission diagnosis who was discharged due to healing of the condition.

Patients were consecutively included as they met the inclusion criteria. The decision on patient treatment site was at the discretion of the emergency department treating physician, without mortality prediction rules implementation having any influence.

Sample size and power

A minimum sample size necessary to identify an odds ratio (OR) different from 1 was established, with an alpha error of 0.05, power of 0.90, four controls per case and considering the Chi-square test without continuity correction. Thus, 38 cases and 152 controls were required¹⁰.

Each case was examined to verify that CAP diagnostic criteria were met, and data were collected in a study-standardized worksheet. Patients were followed during the study period until discharge or outcome of each patient.

The “outcome” variable was in-hospital death. The independent variables were sociodemographic variables, clinical characteristics (comorbidity, symptoms, time with the condition, time between onset of the condition, and treatment initiation), history of influenza and pneumococcus vaccination, pleural effusion, obesity (body mass index [BMI] > 30 kg/m²), and undernutrition (BMI < 18.5 kg/m² for women and < 20 kg/m² for men), usual clinical laboratory tests for these patients, initial antibiotic treatment, isolated microorganisms, and PSI⁶ and CURB-65⁵ severity indices scores. To calculate the PSI score, points are added according to age, gender, presence of comorbidity and alterations found on physical examination and laboratory and radiological investigations. With the obtained score, patients are stratified into categories that range from I to V according to their severity. Class I corresponds to patients younger than 50 years without neoplastic disease, liver disease, congestive heart failure or cerebrovascular or kidney disease, with normal or slightly altered vital signs, and without mental state disorder. Classes II to V are assigned according to three demographic variables (age, gender, and residence at nursing home), five comorbid conditions, five findings on physical examination and seven laboratory or radiographic findings. Risk Class I corresponds to 0 points; Class II, between 1 and 70 points; Class III, between 71 and 90 points; Class IV, between 91 and 130 points; and Class V, more than 130 points.

The CURB-65 scale is based on the evaluation of four essential prognostic variables, in addition to age older than 65 years: confusion, defined as an abbreviated

mental state test score of 8 or less; urea nitrogen $\geq$ 20 mg/dL, respiratory rate $\geq$ 30 bpm and systolic pressure < 90 mmHg or diastolic pressure $\leq$ 60 mmHg.

Each variable present represents 1 point, and patients with two or more of these prognostic factors have a highly elevated risk of death and should be immediately referred to the hospital, since this is an indication for admission to the intensive care unit.

Initial antimicrobial treatment in all cases adhered to international and national clinical practice guidelines for CAP. The most commonly used regimens were third-generation cephalosporin plus macrolide or respiratory fluoroquinolone, both initially by intravenous route. The decision of one regimen or the other was at the discretion of the treating physician and antimicrobials availability at the institution.

Statistical analysis

The STATA 15.1.0 statistical package (College Station, Texas, USA) was used. To summarize the data, descriptive statistics appropriate to each variable were used. Continuous variables were expressed as medians (interquartile range), and categorical variables as frequencies and percentages.

The association of different independent variables (clinical and laboratory) with the outcome variable (in-hospital death) was evaluated by logistic regression according to Hosmer-Lemeshow methodology. Initially, a bivariate analysis was carried out, from which variables were selected according to their statistical significance ($p \leq 0.2$) and biological plausibility, which were included in a multivariate analysis model. Odds ratios were expressed with a 95% confidence interval (CI). To evaluate the model, the goodness-of-fit test was used, and sensitivity, specificity, and predictive values of the model were determined, as well as the area under the curve.

Results

Patients with CAP were included: 87 cases with in-hospital death and 230 controls who were alive at discharge. Cases were older than subjects who were alive at discharge, with a median of 64 versus 55 years, respectively ($p < 0.05$). Age as a continuous and stratified variable was significantly associated with mortality. From age 50 onward, the risk of mortality increases proportionally as age advances: In the 50-70 years stratum, OR was 1.66 (95% CI: 0.89-3), and in those older than 70 years, OR was 2.22 (95%

Table 1. Baseline characteristics of the study population with regard to vital status

Clinical characteristics	Total population (n = 317) n (%)	Cases (n = 87) n (%)	Controls (n = 230) n (%)	OR (95% CI)	p
General					
Age in years, median (25-75 interquartile range)	58 (41-73)	64 (47-79)	55 (38-71)	1.0 (1.0-1.03)	0.006
Age > 50 years	196 (61.8)	63 (72.4)	133 (57.8)	1.91 (1.12-3.28)	0.018
Gender					
Females	144 (45.4)	45 (51.7)	99 (43)	1.41 (0.86-2.32)	0.167
Males	173 (54.6)	42 (48.3)	131 (57)		
Comorbidity					
At least one comorbidity	189 (59.6)	54 (62)	135 (58.7)	1.15 (0.69-1.91)	0.585
Diabetes	87 (27.4)	19 (21.8)	68 (29.6)	0.67 (0.37-1.19)	0.171
Hypertension	96 (30.4)	9 (10.3)	36 (15.7)	0.67 (0.38-1.17)	0.160
Cardiovascular	33 (10.4)	13 (15)	20 (8.7)	1.84 (0.87-3.89)	0.108
Cerebrovascular	43 (13.6)	18 (20.7)	25 (10.9)	2.13 (1.10-4.16)	0.025
Neoplastic	11(3.5)	2 (2.3)	9 (3.9)	0.58 (0.12-2.73)	0.489
Active or former smoker	145 (45.7)	40 (46)	105 (45.7)	1.01 (0.62-1.66)	0.959
Exposure to wood smoke	87 (27.4)	28 (32.2)	59 (25.7)	1.38 (0.80-2.36)	0.246
Prior antibiotic	125 (39.4)	38 (43.7)	87 (37.8)	1.27 (0.78-2.10)	0.342

CI: 1.20-4.12). Among the cases, there were more women than men, with no significant difference. In the overall population, presence of at least one comorbidity (diabetes, hypertension, cerebrovascular disease, etc.) was observed in 189 (59.6%) patients, with no significant differences between cases and controls. Having cerebrovascular disease was associated with mortality (OR: 2.13; 95% CI: 1.10-4.16). There were no differences between cases and controls with regard to history of exposure to tobacco or wood smoke (Table 1).

Crude analysis of clinical signs alterations and laboratory variables association with mortality showed that many were positively associated, such as heart rate > 124 beats/min (b/m), respiratory rate > 30 bpm, total leukocytes > 12,000 mm³, blood urea nitrogen ≥ 30 mg/dL, and arterial pH < 7.35, among others. The respiratory pathogen was identified in 14.2% of total population, with no significant differences between both study groups. PSI class > 3 and a CURB-65 score > 1 were strongly associated with mortality (Table 2).

The multivariate model for mortality showed that stratified age remains strongly associated, as well as other variables such as being female, heart rate > 124 b/m, respiratory rate > 30 bpm, total leukocytes ≥ 12,000 and blood urea nitrogen > 30 mg/dL. Having a history of hypertension persists as a protective variable for mortality in this model (Table 3). Regarding overall evaluation of the model, it met the goodness-of-fit criterion (p = 0.7417), and had a sensitivity of 38.37%, specificity

of 93.48%, a positive predictive value of 68.75%, and negative predictive value of 80.22%. The predictive value of the model, evaluated by the area under the curve was 0.78.

In the distribution of mortality risks for the PSI and CURB-65 indices in the cases of death, a trend that is directly proportional to the frequency of observed mortality as each level of risk increases stands out. In addition, we documented that, of the entire study sample, 113 (35.6%) patients did not meet the hospitalization criteria according to PSI Classes I and II, and there were 156 (49.2%) with a CURB-65 score of 0 and 1 (Table 4).

Discussion

The model proposed as a mortality predictor for CAP includes seven variables that are easy to document: five of them are easily obtained from the medical record and vital signs evaluation, and the other two are clinical laboratory variables available at any health-care unit. It was shown to be a good model according to the criteria that were studied for its evaluation, such as the goodness-of-fit test and the area under the curve.

In the bivariate analysis, many of the variables that were associated with CAP mortality are those already described in other populations and those included in PSI⁶ and CURB-65⁵ mortality prediction indices, such as neurological and cardiovascular

Table 2. Selected vital signs and clinical laboratory variables with regard to vital status of the study population

	Cases (n = 87) n (%)	Controls (n = 230) n (%)	OR (95% CI)	p
Clinical signs				
Systolic pressure < 90 mmHg	13 (14.9)	17 (7.4)	2.13 (0.99-4.60)	0.054
Heart rate > 124 b/m	19 (21.8)	24 (10.4)	2.39 (1.24-4.65)	0.010
Respiratory rate ≥ 30 bpm	38 (46.7)	48 (20.9)	2.86 (1.68-4.86)	0.001
Pleural effusion	5 (5.8)	37 (16.1)	0.32 (0.12-0.84)	0.020
Clinical laboratory				
Total leukocytes ≥ 12,000/mm ³	56 (64.4)	106 (46.1)	2.11 (1.3-3.5)	0.004
Total leukocytes ≤ 3,500	4 (4.6)	4 (1.7)	2.76 (0.68-11.2)	0.155
Total neutrophils ≥ 9,500	52 (59.8)	107 (46.5)	1.70 (1.03-2.82)	0.036
Hematocrit < 30%	14 (16.1)	16 (7)	2.6 (1.2-5.5)	0.016
Glucose > 250 mg/dL	8 (9.2)	17 (7.4)	1.3 (0.5-3)	0.596
Blood urea nitrogen ≥ 30 mg/dL	42 (48.3)	36 (15.7)	5 (2.9-8.7)	0.001
Sodium < 130 mmol/L	6 (7)	21 (9)	0.74 (0.29-1.89)	0.526
Serum albumin < 3.0 g/dL N/n	66/85 (77.7)	153/289 (73.2)	1.27 (0.70-2.3)	0.429
Arterial pH < 7.35	14 (16.1)	17 (7.4)	2.40 (1.13-5.12)	0.023
SpO ₂ < 88%	63 (72.4)	116 (50.4)	2.57 (1.51-4.41)	0.001
Microbiological identification	14 (16.09)	31 (13.5)	1.23 (0.62-2.45)	0.552
PSI class III	62 (70.1)	75 (32.6)	4.85 (2.84-8.28)	0.000
CURB-65 > 1	65 (74.7)	96 (41.7)	4.12 (2.38-7.15)	0.000

CI: confidence interval; OR: odds ratio; SpO₂: blood oxygen saturation.**Table 3. Community-acquired pneumonia mortality multivariate analysis**

Clinical characteristics	OR (95% CI)	p
Stratified age		
< 50 years	Reference	0.034
50-70 years	2.35 (1.06-5.17)	0.019
> 70 years	2.75 (1.18-6.37)	
Female gender	2.05 (1.11-3.8)	0.021
Hypertension	0.40 (0.20-0.80)	0.010
Heart rate > 124 b/m	2.68 (1.16-6.17)	0.021
Respiratory rate > 30 bpm	2.85 (1.54-5.29)	0.001
Total leukocytes ≥ 12,000	2.17 (1.21-3.87)	0.009
Blood urea nitrogen > 30 mg/dL	4.85 (2.55-9.24)	0.000

CI: confidence interval; OR: odds ratio.

comorbidity, clinical signs such as heart rate > 124 b/m, respiratory rate > 30 bpm, and systolic blood pressure < 90 mmHg, as well as laboratory variables such as blood urea nitrogen > 30 mg/dL and hematocrit < 30%¹¹. Other variables not included in said prediction indices, such as total leukocytes > 12,000 and total neutrophils > 9500, were also associated in our population. Albumin was not associated with mortality in our study and pleural effusion was a protective factor (OR: 0.32; 95% CI: 0.12-0.84) for CAP mortality. In contrast, in the CURB-65 prediction rule validation study, albumin and pleural effusion were associated with mortality in the bivariate analysis, although only few subjects were evaluated

Table 4. Risk distribution and mortality observed for PSI and CURB-65 in the entire population and in deceased cases

Severity	Total population (n = 317) n (%)	Deaths (n = 87) n (%)
PSI Class I	52 (16.4)	3 (5.8)
PSI Class II	61 (19.2)	7 (11.5)
PSI Class III	68 (21.5)	16 (23.5)
PSI Class IV	94 (29.6)	39 (41.5)
PSI Class V	42 (13.3)	22 (52.4)
CURB 0	80 (25.2)	10 (12.5)
CURB 1	76 (24)	12 (15.8)
CURB 2	88 (27.8)	31 (35.2)
CURB 3	55 (17.4)	23 (41.8)
CURB 4	16 (5)	9 (56.3)
CURB 5	2 (0.63)	2 (100)

for those variables⁵. In addition, a class > III PSI and CURB-65 > 1 point are also useful, given that both were strongly associated with mortality, with ORs of 4.85 (95% CI: 2.84-8.28) and 4.12 (95% CI: 2.38-7.15), respectively, which suggests that the risk profile of our population, in general terms, is not different from the scenario these prediction rules were derived from, which positively impacts on their validity.

The multivariate model further confirms the observation that age older than 50 years is a strong predictor of mortality, together with other variables such as being a female and having total leukocytes $\geq 12,000$. A history of hypertension behaves as a protective variable for mortality in this model. Regarding the latter variable, the only explanation we have is that it may be due to the opposite effect hypotension has as a risk factor, and we consider this to be biologically plausible. This, as far as we know, is something not previously described that deserves to be explored, given that it persists when adjusted for other variables such as age and precisely in subjects older than 50 years is the prevalence of a history of high blood pressure much higher than in those younger than 50 years (42.6 vs. 10.7%).

With the purpose to improve the outcome of patients who suffer from CAP, since 1993, some medical societies of the United States of America and other parts of the world developed different clinical guidelines for the care of these patients²⁻⁴, in which recommendations are proposed for the diagnosis, treatment and prevention of CAP, the compliance of which has shown a positive impact on the outcome. However, there is still the problem of deciding which patients to hospitalize and which can be treated on an outpatient basis, which unquestionably has an impact on the costs of care.

Prognostic prediction indices, such as PSI and CURB-65, although validated for mortality, are mainly used to identify cases of lower risk and that can be treated on an outpatient basis without increasing the risk of death. For PSI, indications say that patients in Classes I and II generally do not require hospitalization, those in Class III may require very brief hospitalization, and those in Classes IV and V generally require hospitalization. In the case of CURB-65, hospitalizing those who have 2 points or more is recommended. However, hospitalization of patients classified as of low risk for various reasons is highly common. In our study, 35.6% and 49.2% of cases had no hospitalization criteria according to PSI and CURB-65, respectively, a proportion that is within the figures described by other authors. In the CAPO international medical care quality trial, 26% of cases did not meet the hospitalization criterion according to PSI¹², and other studies have found rates of between 31% and 62.5% for this indicator^{7,8}. The reasons for hospitalization in most our patients who did not require hospitalization according to PSI and CURB-65 criteria included hypoxemia, need to treat any comorbidity, parapneumonic pleural effusion, bilateral multilobar

radiological compromise, or oral intolerance. However, in many cases, a higher need for hospitalization is likely to have been estimated. In this regard, there is evidence that in approximately 20% of hospitalized cases with low risk for mortality, no reason for it is documented, except for the decision of the treating physician¹³. This is an aspect that should be evaluated in our institution given its characteristics, and although PSI is a good predictor of mortality risk at hospital admission, it may not be useful in some cases, since it does not take into account social-type factors or the need to treat another comorbidity (Table 4).

The limitations of this study include its case-control design and sample size, compared to the large cohorts the prediction indices were derived from; in addition, there was no follow-up after discharge and the results do not apply to outpatients. We were unable to assess the contribution of pneumococcal vaccination history due to a lack of information on the subject.

Conclusions

In the proposed risk model, age older than 50 years, being a female, heart rate > 124 b/m, respiratory rate > 30 bpm, leukocytes $> 12,000$, and blood urea nitrogen > 20 mg/dL were positively associated with mortality. A history of hypertension was protective for mortality. The variables of the model are easy to document with the medical record and usual laboratory tests in hospitalized patients with CAP.

A high frequency of hospitalized patients with low-risk criteria according to PSI and CURB-65 stands out: 35.6% and 49.2%, respectively

Funding

The authors received no sponsorship for the development of this manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

References

1. Soto-Estrada G, Moreno-Altamirano L, Pahua-Días D. Panorama epidemiológico de México, principales causas de morbilidad y mortalidad. *Revista de la Facultad de Medicina de la UNAM*. 2016;59:8-22.
2. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumoniae. *Am J Respir Crit Care Med*. 2001;163:1730-54.
3. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(Suppl 2):S27-S72.
4. Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J*. 2005;26:1138-80.
5. Lim WS, Lewis S, Macfarlane T. Severity prediction rules in community acquired pneumonia: a validation study. *Thorax*. 2000;55:219-23.
6. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *New Engl J Med*. 1997;336:243-50.
7. Yealy DM, Auble TE, Stone RA, Lave JR, Meehan TP, Graff LG, et al. Effect of increasing the intensity of implementing pneumonia guidelines: a randomized, controlled trial. *Ann Intern Med*. 2005;143:881-94.
8. Atlas SJ, Benzer TI, Borowsky LH, Chang Y, Burnham DC, Metlay JP, et al. Safely increasing the proportion of patients with community-acquired pneumonia treated as outpatients: an interventional trial. *Arch Intern Med*. 1998;158:1350-6.
9. Báez Saldaña R, Gómez-Zamora C, López-Elizondo C, Molina-Corona H, Santillán Martínez A, Sánchez-Hernández J, et al. Neumonía adquirida en la comunidad. Revisión y actualización con una perspectiva orientada a la calidad de la atención médica. *Neumol Cir Torax*. 2013;72(Supl 1):6-43.
10. Chow S, Shao J, Wang H. Sample size calculations in clinical research. 2nd ed. Chapman & Hall/CRC Biostatistics Series; 2008. p. 106.
11. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky S, Kapoor WN, et al. Causes of death for patients with community-acquired pneumonia. *Arch Intern Med*. 2002;162:1059-64.
12. Ramírez JA. Community-Acquired Pneumonia Organization Investigators. Worldwide perspective of the quality of care provided to hospitalized patients with community-acquired pneumonia: results from the CAPO international cohort study. *Semin Respir Crit Care Med*. 2005;26:543-52.
13. Labarere J, Stone RA, Obrosky S, Yealy DM, Meehan TP, Auble TE, et al. Factors associated with the hospitalization of low-risk patients with community-acquired pneumonia in a cluster-randomized trial. *J Gen Intern Med*. 2006;21:745-52.