In-hospital mortality risk factors in community acquired pneumonia: evaluation of immunocompetent adult patients without comorbidities

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Summary

Introduction: several scores were developed in order to improve the determination of community acquired pneumonia (CAP) severity and its management, mainly CURB-65 and SACP score. However, none of them were evaluated for risk assessment of in-hospital mortality, particularly in individuals who were non-immunosuppressed and/or without any comorbidity. In this regard, the present study was carried out.

Methods: we performed a cross-sectional study in 272 immunocompetent patients without comorbidities and with a diagnosis of CAP. Performance of CURB-65 and SCAP scores in predicting in-hospital mortality was evaluated. Also, variables related to death were assessed. Furthermore, in order to design a model of in-hospital mortality prediction, sampled individuals were randomly divided in two groups. The association of the variables with mortality was weighed and, by multiple binary regression, a model was constructed in one of the subgroups. Then, it was validated in the other subgroup.

Results: both scores yielded a fair strength of agreement, and CURB-65 showed a better performance in predicting in-hospital mortality. In our casuistry, age, white blood cell counts, *serum urea* and diastolic blood pressure were related to death. The model constructed with these variables showed a good performance in predicting in-hospital mortality; moreover, only one patient with fatal outcome was not correctly classified in the group where the model was constructed and in the group where it was validated.

Conclusion: our findings suggest that a simple model that uses only 4 variables, which are easily accessible and interpretable, can identify seriously ill patients with CAP.

Keywords: pneumonia, in-hospital mortality, risk factors.

Study conducted at the Internal Medicine Service, Hospital J. B. Iturraspe, Santa Fe, Argentina

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Introduction

Community acquired pneumonia (CAP) is one of the most common infectious causes of death in the world[1] with a mortality rate of 1% in outpatient departments and higher than 50% in hospitalized patients.[2,3] One of the most important reasons of the high rate of this adverse outcome is suboptimal management, regarding antibiotic treatment, or in relation to the identification of individuals with requirement of intensive care unit admission. Early identification of risk factors in these patients allows earlier intervention and, thus, improvement of the outcomes.[4-6]

Using clinical judgment, physicians may both overestimate and underestimate the severity of CAP, leading to inappropriate hospitalization for mild cases that could be treated at home, or insufficiently aggressive interventions for patients at high risk of complications.[6-14] Then, severity scores may provide objective classification of patients. The British Thoracic Society recommends the use of a simple prediction tool based on short-term mortality, the CURB-65 score system.[9] This score, composed of only five variables, is significantly easier to remember and use. Nevertheless, several studies have produced conflicting results in relation to its performance.[10, 14] Other score system recently pub-

lished is the SCAP (severity community acquired pneumonia) score, which showed better efficacy than the CURB-65 in defining patients with high risk of adverse outcome.[10,14] Both scores are widely used and recommended in clinical practice guidelines for CAP management.[9-11,14]

However, to our knowledge, none of them were evaluated for risk assessment of in-hospital mortality, particularly in individuals who were non-immunosuppressed and/or without any comorbidities.[6-16] In this regard, the present study was carried out.

Materials and methods

Study population and subject evaluation

We performed a cross-sectional study with duration of three years, from 2010 to 2013, including 272 adult patients diagnosed with community acquired pneumonia (CAP) who were admitted in the Clinical Department of the Iturraspe Hospital (Santa Fe, Argentina). The hospital provides its services to low income people who cannot afford private coverage, and it has 40 beds for admission in the clinical sector.

CAP diagnosis was defined by clinical features (e.g., cough, fever, pleural chest pain) plus pulmonary infiltrates on chest radiograph or computed tomography not known to be old. Individuals were subjected to a complete clinical examination, including chest X-ray, and biochemical tests. Exclusion criteria comprised: age > 18 years, hospitalization for the previous 14 days, coronary artery disease or history of other cardiac diseases, chronic renal disturbances, thyroid disease, co-infection with HIV, immunosuppression or ongoing use of immunosuppressant agents, diabetes, chronic obstructive pulmonary disease, chronic suppurative lung disease (bronchiectasis, cystic fibrosis), nosocomial pneumonia or health care-associated pneumonia, suspected aspiration pneumonia and other systemic complaints.

Both CURB-65 and SCAP scores were applied to all the individuals. Patients were then classified by CURB-65 score as low, intermediate or high risk, e.g. classes 0 to 1, class 2 and classes 3 through 5, respectively,[9] and by SCAP score as low risk (0 to 9 points), intermediate risk (10 to 19 points) and high risk (≥ 20 points).[10, 14] In addition, we assessed if the patients met sepsis and severe sepsis criteria, defined according to the American College of Chest Physicians and Society of Critical Care Medicine.[17]

The study was approved by the Ethics Review Board of the Hospital. Informed consent was obtained from all participants. All patients were treated empirically with antibiotics, according to local practice and international established guidelines.

Statistical analysis

Data were analyzed by using MedCalc version 12.2.1. Normal distributions of the continuous variables were tested using Kolmogorov-Smirnov method. The data are expressed as mean ± SD or median and interquartile range. Groups were compared in relation to age, sex and CAP severity. The association of the variables with in-hospital mortality was assessed. Chi-square test or Fisher's exact test were used for categorical variables, whereas the one-way Anova (Student-Newman-Keuls post-hoc test for all pairwise comparisons) or Student's *t*-test were used to compare means. Receiver operating characteristic (ROC) curve was conducted for each score and variable related to in-hospital mortality.

In order to design a model for in-hospital mortality prediction, sampled individuals were randomly divided in two groups (A and B) with 136 individuals each. In subgroup A, association of the variables with mortality was assessed as described previously. Then, considering the optimal criterion of the variables related to death by ROC curve, we categorized them in binomial and constructed a model using multiple binary logistic regression for predicting in-hospital mortality. The Hosmer-Lemeshow test was employed for goodness of fit of the logistic regression model. Finally, the model was validated in subgroup B.[18-20] A p value < 0.05 was considered significant.

Results

General population

The whole sample was composed of 131 males and 141 females aged 52±17.3 years (mean ± SD). There was no age difference between sex-distribution. Thirty six patients required admission in the Intensive Care Unit (ICU) due to requirement of mechanical ventilation, and 23 died while in-hospital (5 of those admitted in ICU). The mean age of the patients who died was 70.6±12.2 years (range 43-89). Of the whole sample, 206 individuals met sepsis criteria and 22 of severe sepsis. In regard to the CURB-65 and SCAP score, there were 72, 156 and 44, and 160, 99 and 13 patients stratified in low, intermediate and high risk, respectively. The features of the patients from each group of CURB-65 and SCAP scores are summarized in Tables 1 and 2.

Patients who died were older (p=0.003) and presented higher levels of white blood cell counts (WBC) and *serum urea* (p<0.001), and lower diastolic blood pressure (p=0.05). There was no difference in heart rate, respiratory frequency, systolic blood pressure, arterial blood pH and pO_2, pCO_2 and *serum* glycemia. Also, there was no relation between mortality and intensive care unit admission, sepsis, bacteremia or patterns of pulmonary infiltrates.

TABLE 1 Characteristics of the patients used to derive CURB-65 score. Quantitative variables are expressed as mean ± SD.

	Low risk (n=72)	Intermediate risk (n=156)	High risk (n=44)	p
Age	43.9±11.8	51.3±11.2	67.7±13.4[1]	<0.001
Gender (n)				
Male	36	73	22	NS
Female	36	83	22	
Systolic blood pressure	123.8±15.5 mmHg	117.2±16.4 mmHg	106±20[2] mmHg	0.001
Diastolic blood pressure	77.6±8 mmHg	70±10 mmHg	60±5[3] mmHg	<0.001
Heart rate	95±17	104±18	101±24	NS
Respiratory frequency	23±3[4]	29±7	31±8	<0.001
Sepsis (n)				
Non-septic	18	19	7	<0.05
Sepsis	54	122[5]	30	
Severe sepsis	-	15[6]	7	
Admission in the Intensive Unit Care **(n)**	6	23[7]	7	0.001
Mortality rate **(n)**	1[8]	9	13	0.001

NS: Not significant
Patients in the high risk group were older than the remaining ones[1] and had lower levels of systolic[2] and diastolic blood pressure.[3] Compared with low risk patients, all the groups presented higher respiratory frequency.[4] The highest proportions of sepsis[5] and severe sepsis[6] were found in the intermediate risk. Also, this group presented the higher casuistic of patients admitted into the ICU unit.[7] In regard to mortality rate, it was increased in those patients stratified as intermediate and high risk.[8]

TABLE 2 Characteristics of the patients used to derive SCAP score. Quantitative variables are expressed as mean ± SD.

	Low risk (n=160)	Intermediate risk (n=99)	High risk (n=13)	p
Age	49.5±13.1	55.4±18.5	57.3±19.5	NS
Gender (n)				
Male	70	58	3[1]	<0.0001
Female	90	41	10[1]	
Systolic blood pressure	120.3±17.7 mmHg	115.6±18.3 mmHg	94.2±16.4	NS
Diastolic blood pressure	72.8±12.7 mmHg	69.1±10.3 mmHg	55.3±12.6 mmHg	NS
Heart rate	98±18	107±20	100±23	NS
Respiratory frequency	25±5[2]	32±8	34±4	<0.001
Sepsis (n)				
Non-septic	35	8	1	<0.05
Sepsis	125[3]	77	4	
Severe sepsis	-	4	8	
Admission in the Intensive Unit Care **(n)**	16	15	5[4]	0.01
Mortality rate **(n)**	9	12	2[4]	0.01

NS: Not significant
[1] The proportion male to female in the high risk group was lower than in the other risk categories.
[2] Compared with low risk, all the remaining groups presented higher respiratory frequency.
[3] Also, this group presented the higher casuistic of patient with sepsis.
[4] Despite 13 patients were classified as high risk by the SCAP score, this group presented lowest requirement of ICU admission and mortality rate.

Prediction of in-hospital mortality by the severity scores

The rates of mortality in each of the CURB-65 classes were: for class I, 1; class II, 9; and class III, 13. For SCAP score, rates were: for class 1, 9; class 2, 12; and class 3, 2. Considering these data, we performed an Inter-Rate Agreement (Kappa) with both scores, which yielded a fair strength of agreement (weighted kappa =0.27, 95% CI 0.24-0.4, p<0.001, Table 3). Furthermore, we analyzed the agreement between sepsis criteria and both community acquired pneumonia severity scores. Neither CURB-65 nor SCAP score presented good agreement index with sepsis stratification (Kappa of 0.1, p=0.003, and 0.09, p=0.02, respectively).

The ROC curve of CURB-65 for mortality yielded an area under the curve (AUC) of 81% (95% CI 76-85, p<0.001) for one criterion positive, with sensitivity of 91.3% (95% CI: 72-98.9), specificity of 61% (95% CI: 54.7-67.1) and LR of 2.3. Conversely, the ROC curve of SACP for mortality

was 66% (95% CI 60-71, p=0.003) for 11 points, with sensitivity of 52.1% (95% CI: 30.6-73.2), specificity of 70.3% (95% CI: 64.2-75.9) and LR of 1.8. The difference between areas of the ROC curves for mortality by both scores was 0.15 (95% CI 0.04-0.2, p=0.006), yielding a better predictive value the CURB-65 score.

TABLE 3 Inter Rate Agreement (Kappa) between both scores for community acquired pneumonia. Weighted kappa =0.27, 95% CI 0.24 to 0.4, p<0.001.

SCAP score	CURB-65 score			
	Low risk	Intermediate risk	High risk	
Low risk	68	81	11	160 (58.8%)
Intermediate risk	4	71	24	99 (36.4%)
High risk	0	4	9	13 (4.8%)
	72 (26.5%)	156 (57.4%)	44 (16.2%)	

Prediction model for in-hospital mortality in subgroup A

As mentioned before, the sampled individuals were randomly divided in two groups (A and B) of 136 individuals each.

Group A was composed of 67 males and 68 females aged 52±16.7 years (mean ± SD). There were no age differences between sex-distribution. One hundred and fourteen patients met sepsis criteria (9 of severe sepsis), 16 individuals required admission in the Intensive Care Unit (ICU) due to requirement of mechanical ventilation, and 14 individuals died while in-hospital. The mean age of the patients who died was 63.8±14.1 years (range 45-89), these individuals were older than the remaining of the group (p=0.02). Neither ICU admission nor sepsis were related to death (Chi-squared 0.1, p=0.08, and 0.18, p=0.09, respectively).

As it was observed in the whole sample, patients who died presented increased levels of white blood cells (p<0.0001), *serum urea* (p<0.0001) and decreased values of diastolic blood pressure (p<0.0001). No other variables, as described previously for all individuals, were related to in-hospital mortality. We then evaluated the ROC curve of the variables associated to death, obtaining for the variable age an area under the curve (AUC) of 79% (95%CI 61.3-87.7, p=0.01) with a cutoff of 70 years, with sensitivity of 40% (95%CI 26.2-73.8), specificity of 87.3% (95%CI 80.2-92.6) and a LR of 3. In the case of WBC, the AUC was 85.8% (95%CI 78.7-91.2, p<0.0001), with an optimal criterion of 21,000 cells/mm^3 with sensitivity of 80% (95%CI 44.4- 97.5), specificity of 80.9% (95%CI 78- 88.1) and a LR of 4. *Serum urea* presented an AUC of 75.5% (95%CI 76-86, p<0.0001) for a *urea* level of 0.57 g/L with sensitivity of 70% (95%CI: 34.8-81.3), specificity of 84.9% (95%CI 77.5-90.7) and a LR of 3. Finally, the AUC of diastolic blood pressure was 67% (95%CI 51.9-68.9, p=0.02) for 60 mmHg, sensitivity of 60% (95%CI 44.4-87.8), specificity of 67.4% (95%CI 58.5-75.5) and a LR of 2.

Considering the optimal criterion of the variables by ROC curve, we categorized them in binomial and constructed a model by a multiple binary logistic regression for predicting in-hospital mortality. The overall model fit Chi-squared was 27.4 (p<0.0001) with a Hosmer & Lemeshow test of 1.41, p=1, indicating a good logistic regression model fit. The odd ratios were: age 5 (95%CI 1.68-17.7 p=0.01), *serum urea* 7 (95%CI 2.36-14.6, p=0.02), diastolic blood pressure 2 (95%CI 1.36-6, p=0.01) and WBC 18 (95%CI 15.3-24.6, p=0.001). The percent of cases correctly classified within the group A by this model was 92.85% (n=13). The AUC was 95.3% (95%CI 84.2-97.8, p<0.0001) for a criterion of 20 points, sensitivity of 80% (95%CI 69.2-97.5) and a specificity of 91.3 (95%CI 84.9-95.6).

Assessment of in-hospital mortality risk by the constructed model in the subgroup B

The mean age was 52.3±17.2 years, and there were no age differences between sex-distribution. Besides, there was no difference compared to group A in relation to age, gender, rate of in-hospital mortality, sepsis and requirement of ICU admission. With the results of the multiple binary logistic regression, using the odd ratios of each variable to construct a score of 32 points, we conducted a ROC curve analysis for predicting in-hospital mortality. The AUC was 98% (95%CI 94.8-99.8, p<0.0001) with an associated criterion of 20, sensitivity of 92.3% (95%CI 64.8-99.8) and specificity of 95.1% (95%CI 89.7-98.2). Comparisons between the ROC curves of the constructed model in groups A and B yielded no statistical differences. Furthermore, as it was observed in group A, only one individual who died was not correctly classified.

Discussion

Community acquired pneumonia is one of the largest causes of death from infectious diseases worldwide. A scoring system to accurately assess the severity of pneumonia was developed in order to apply the adequate antibiotic treatments.[1, 2, 9, 10] Several studies observed different but positive correlations between the severity determined by the scores and short-term mortality rates. However, other works have

concluded that the score systems have different strengths and weaknesses, depending on the studied population and the analyzed outcome.[11, 15,21-27] We observed in our casuistry that these score systems had fair strength of agreement with important difference between them in classifying CAP severity, similar to reported data.[21-27]

In our study, CURB-65 and the SCAP scores were applied in order to assess if they might be useful to predict in-hospital mortality. In this regard, CURB-65 score had a better performance than the SCAP score with an area under the ROC curve of 81%, which is comparable to the results of other studies.[4,11,23-27] Contrariwise, SCAP score presented a regular area under the ROC curve; moreover, 52% of the individuals who died were stratified as intermediate risk. This percentage of dead individuals classified as intermediate risk is higher than the ones observed elsewhere.[10,15,26-31]

We observed that the variables age, *serum urea* level and diastolic blood pressure, which are part of both scores,[9,10,14] showed a good correlation with in-hospital mortality. But WBC in our sampled individuals was also related to the fatal outcome as previously reported by Bircan et al.,[32] who have observed that WBC might be useful for predicting adverse outcome in patients with CAP. As a last attempt using the variables related to death, we performed and validated a model with high performance in classifying individuals in terms of in-hospital mortality. This model might be useful to define those patients with requirement of major medical care.

Finally, the differences observed in this study, compared with others in relation to the risk factor for in-hospital mortality due to CAP,[23-31] might be mainly due to characteristics of the sampled individuals studied. As previously mentioned, in order to evaluate the endpoint in patients not immunosuppressed and without major comorbidities, we excluded patients with cancer, chronic renal failure, COPD, diabetes and the presence of immunosuppression, which are variables highly related to mortality. Our findings suggest that a simple model that uses only 4 variables, which are easily accessible and interpretable, can identify seriously ill patients with community acquired pneumonia.

Conclusion

Our results suggest that although the common scores CURB-65 and SCAP are widely used, they might not be useful for predicting in-hospital mortality. However, the variables *serum urea*, age and diastolic blood pressure, which are used to determine both scores, were related to death. In addition, we observed that white blood cell count in our casuistry was also associated with the fatal outcome. A model with the four variables showed a better performance in identifying seriously ill patients with CAP.

Limitation of the study

Our cross-sectional study was performed in a single-center with a relatively reduced sample size. Prospective multicentric studies with different individual profiles will help to ascertain which variables have a better performance in predicting adverse outcomes in patients with community acquired pneumonia.

Resumo

Fatores de risco para mortalidade intra-hospitalar em pneumonia adquirida em comunidade: avaliação de pacientes imunocompetentes sem comorbidades.

Introdução: diversos escores de gravidade da pneumonia adquirida em comunidade (PAC) foram desenvolvidos com o intuito de melhorar o manejo clínico, em especial os escores CURB-65 e SCAP. Contudo, nenhum dos dois foi avaliado para determinar o risco de morte intra-hospitalar, principalmente em pacientes imunocompetentes e/ou sem comorbidades. Diante disso, propusemo-nos a analisar a utilidade dos escores para prever a mortalidade intra-hospitalar e estudar as variáveis associadas ao desfecho fatal.
Métodos: desenvolvemos um trabalho transversal com 272 pacientes imunocompetentes, sem comorbidades e com diagnóstico de PAC. Foi avaliada a eficácia dos escores CURB-65 e SCAP em prever a mortalidade durante a internação. Foram estudadas as variáveis relacionadas a este desfecho. Por fim, a amostra foi dividida em dois subgrupos com o objetivo de desenvolver um modelo de avaliação do risco de morte em um subgrupo, validando-o no outro.
Resultados: ambos os escores apresentaram pobre concordância de classificação da gravidade para PAC. O escore CURB-65 mostrou melhor desempenho na avaliação do risco de morte. Em nossa amostra, idade, contagem de glóbulos brancos, ureia sérica e pressão arterial diastólica foram as variáveis que se associaram à mortalidade. O modelo desenvolvido com essas variáveis mostrou eficácia muito boa para prever o desfecho fatal. Inclusive, somente um paciente no grupo de desenvolvimento do modelo e outro no grupo de validação foram classificados de modo incorreto.
Conclusão: nossos resultados sugerem que com um modelo de quatro variáveis, de fácil acesso e interpretação, foi possível identificar pacientes gravemente enfermos com PAC.

Palavras-chave: pneumonia, mortalidade intra-hospitalar, variáveis de risco.

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