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SHORT COMMUNICATION

Combined use of the multidimensional prognostic index (MPI) and procalcitonin serum levels in predicting 1-month mortality risk in older patients hospitalized with community-acquired pneumonia (CAP): a prospective study

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Abstract
Background Several scores and biomarkers, i.e., procalcitonin (PCT), were proposed to stratify the mortality risk in community-acquired pneumonia (CAP).
Aim Evaluating prognostic accuracy of PCT and Multidimensional Prognostic Index (MPI) for 1-month mortality risk in older patients with CAP.
Methods At hospital admission and at discharge, patients were evaluated by a Comprehensive Geriatric Assessment to calculate MPI. Serum PCT was measured at admission and 1, 3, and 5 days after hospital admission.
Results 49 patients were enrolled. The overall 1-month mortality was 44.5 for 100-persons year. Mortality rates were higher with the increasing of MPI. In survived patients, MPI at discharge showed higher predictive accuracy than MPI at admission. Adding PCT levels to admission MPI prognostic accuracy for 1-month mortality significantly increased.
Conclusion In older patients with CAP, MPI significantly predicted 1 month mortality. PCT levels significantly improved the accuracy of MPI at admission in predicting 1-month mortality.

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Keywords Community-acquired pneumonia · Elderly · Procalcitonin, Multidimensional prognostic index

Introduction

Community-acquired pneumonia (CAP) is common in older people, ranging from 25 to 44 cases per 1000 persons in patients older than 65 years and over 50 cases per 1000 persons in subjects older than 85 years [1]. CAP is associated with increased risk of re-hospitalization, loss of functional autonomy, and high mortality rates [2].

The severity of CAP and its economic impact has led to the development of disease-specific predictive-score systems, i.e., pneumonia severity index (PSI) and CURB-65 (confusion, blood urea nitrogen, respiratory rate, systolic or diastolic blood pressure, and age >65), to stratify the risk of mortality.

Recently, it was suggested that the prognosis of older patients with chronic and acute diseases is affected by several functional, cognitive, and nutritional factors not directly related to primary disease and that the prognostic model for mortality for these patients should be multidimensional in nature [3]. Recently, we developed and validated a multidimensional prognostic index (MPI) to identify older patients with a different risk for short- and long-term mortalities [4] based on a Comprehensive Geriatric Assessment (CGA) routinely carried out in geriatric wards. The MPI demonstrated good accuracy and excellent calibration in predicting mortality in older patients affected by several diseases [5], including CAP, in which the MPI showed higher accuracy than PSI to predict short- and long-term mortalities [6].

Recently, procalcitonin (PCT), a calcitonin precursor, was reported as a useful biological marker of severity and

prognosis of CAP [7], even in older patients. PCT differs from other proposed sepsis markers, i.e., C-reactive protein and cytokines, because it better reflects the severity of the systemic inflammatory response to infection, and it permits to differentiate between infectious and sterile causes of systemic inflammation [8].

Aim of this study was to evaluate the prognostic accuracy of PCT in comparison with and in addition to MPI to predict 1-month all-cause mortality risk in older patients hospitalized with CAP.

Materials and methods

Patients

All consecutive patients admitted with diagnoses of CAP from February to July 2014 to our Geriatrics unit were screened for eligibility. Inclusion criteria were: (1) age ≥65 years; (2) diagnosis of CAP; (3) ability to provide an informed consent to participate in the study; (4) complete CGA during hospitalization; and (5) availability of mortality/survival information after 1 month from the hospitalization. At baseline, the following parameters were collected by a structural interview and clinical evaluation: date of birth, gender, clinical history, current pathologies, and medication history. All patients received a CGA at admission and discharge. Serum samples were taken at admission and 1, 3, and 5 days after the hospitalization to measure PCT. Vital status after the 1-month follow-up period was assessed by contacting the participants or consulting the Registry Offices of the cities, where the patients were residents.

Diagnosis of pneumonia

CAP was diagnosed using standard criteria, including chest radiograph demonstrating pneumonia, probable pneumonia, or the presence of a new infiltrate and the presence of at least two of the following symptoms and signs compatible with pneumonia: new or increased cough, new or increased sputum production, fever ≥38 °C, pleuritic chest pain, new or increased physical findings on chest examination (rales, rhonchi, wheezes, and bronchial breathing malaise), or difficulty in breathing [9].

The multidimensional prognostic index (MPI)

A CGA was carried out evaluating functional status by Basal and Instrumental Activities of Daily Living, cognitive status by Short Portable Mental Status Questionnaire, nutritional status by Mini Nutritional Assessment, risk of developing pressure sores by Exton-Smith Scale, comorbidities by the Cumulative Illness Rating Scale, the number of drugs at admission, and co-habitation status. The MPI was calculated by the inclusion of information from the above-reported eight domains of the CGA according to the methodology previously reported [4] and expressed with a final MPI score from 0 to 1. For analytical purposes, absolute values of MPI were not considered, but we preferred to express the index as MPI-1 low risk (MPI value ≤0.33), MPI-2 moderate risk (MPI value between 0.34 and 0.66), and MPI-3 severe risk of mortality (MPI >0.66) as previously reported. The approximate time required for collecting data for the CGA was 20 min [4].

Statistical analysis

Patients' baseline characteristics were reported as mean ± standard deviation or frequencies and percentage for continuous and categorical variable. Distribution assumption was checked by means of *Q*–*Q* plot, Shapiro–Wilks and Kolmogorov–Smirnov tests. Baseline comparison between men and women was made using the Chi-squared test for categorical variable and the Mann–Whitney *U* test for continuous variable. Test for linear trend across MPI groups was assessed using linear regression models (where categorical MPI was considered as continuous variable) or Mantel–Haenszel Chi-square test categorical variables, respectively. Rank analysis was performed when skewness was present in continuous variables' distribution. Incidence rate for 100-persons month were also reported and compared using Poisson model. Univariable and multivariable Cox regression models were performed, within 1-month of follow-up, to assess the prognostic effect of the MPI and PCT evaluated at admission and after 1–3–5 days from admission, on 1-month mortality prediction. Results were reported as hazard ratios along with their 95% confidence intervals. For the MPI only, HRs were referred for each increment of 0.10 MPI units. To evaluate improvements in model's discriminatory power provided by PCT (evaluated at admission and after 1–3–5 days from admission) on the MPI, risk probabilities were derived from multivariable Cox regressions. Models' discrimination, i.e., the ability to distinguish subjects who will develop the event from those who will not, was assessed by computing the modified C-statistic for censored survival data. Comparison between C-statistics was carried out following Pencina and D'Agostino's approach. Improvement in predicted risk probabilities between events and non-events was evaluated using Integrated Discrimination Improvement. A p value <0.05 was considered for statistical significance. Analyses were performed using SAS Release 9.3.

Results

Characteristic of the study population

Table 1 shows clinical and functional characteristics of patients according to gender. The study population included 49 patients, 24 men, and 25 women. Women were older and had significantly higher MPI scores than men, both at admission ($p=0.004$) and at discharge ($p=0.032$). No significant differences between men and women were observed in PCT levels, length of stay, comorbidities, and antibiotic therapies. The 1-month all-cause mortality rate was 44.5 for 100-persons month.

MPI scores, procalcitonin levels, and mortality

Univariable Cox regression analysis (Table 2) showed that both MPI at admission ($p=0.025$) and MPI at discharge ($p<0.001$) were significantly associated to 1-month mortality. MPI at discharge demonstrated a significantly higher accuracy in predicting mortality than MPI at admission (survival C-statistic at discharge 0.84 vs survival C-statistic at admission 0.65).

MPI at admission achieved a discriminatory power close to discriminatory power of PTC levels. Adding PTC value (evaluated at admission) into the prognostic model which included MPI at admission, the discriminatory power in predicting mortality improved with a C-statistic increase from 0.65 to 0.69, and achieving a significant increase in the Integrated Discrimination Improvement of 0.045 ($p=0.020$). Similar results were obtained including PTC levels evaluated 1, 3, and 5 days after hospital admission into the prognostic model of MPI at admission (Table 3). Conversely, no improvement was observed when adding PTC values into the prognostic model with MPI at discharge.

Discussion

This study confirmed that MPI was a significant prognostic tool to predict 1-month mortality in hospitalized older

Table 1 Characteristics of the study population divided according to gender

Variable	All patients	Men	Women	*p* value[#]
Number of patients (%)	49 (100%)	24 (49%)	25 (51%)	
Age (years)*	86.59 ± 7.07	84.19 ± 7.80	88.89 ± 5.52	0.018[§]
Length of stay (days)*	8.92 ± 5.25	10.00 ± 6.28	7.88 ± 3.88	0.184
MPI at admission*	0.65 ± 0.20	0.56 ± 0.19	0.73 ± 0.18	0.004
MPI at hospital discharge*	0.69 ± 0.23	0.62 ± 0.22	0.75 ± 0.22	0.032
PCT at admission (ng/mL)[^]	0.32 (0.13–1.08)	0.53 (0.20–2.35)	0.18 (0.13–0.53)	0.101
PCT at first day (ng/mL)[^]	0.52 (0.21–2.83)	0.70 (0.25–6.74)	0.52 (0.16–2.83)	0.558
PCT at third day (ng/mL)[^]	0.45 (0.18–2.19)	0.55 (0.23–4.19)	0.33 (0.09–1.99)	0.246
PCT at fifth day (ng/mL)[^]	0.27 (0.13–0.62)	0.26 (0.15–0.62)	0.27 (0.10–0.70)	0.667
Comorbidity				
Hypertension, *n* (%)	32 (65.3%)	14 (58.3%)	18 (72%)	0.377
Diabetes, *n* (%)	11 (22.4%)	4 (16.7%)	7 (28%)	0.496
Heart failure, *n* (%)	23 (46.9%)	9 (37.5%)	14 (56%)	0.256
Antibiotic therapy				
Cephalosporins, *n* (%)	21 (42.9%)	11 (45.8%)	10 (40%)	0.776
Quinolones, *n* (%)	11 (22.4%)	5 (20.8%)	6 (24%)	1.000
Macrolides, *n* (%)	5 (10.2%)	4 (16.7%)	1 (4%)	0.189
Beta-lactam, *n* (%)	20 (40.8%)	10 (41.7%)	10 (40%)	1.000
Aminoglycosides, *n* (%)	6 (12.2%)	3 (12.5%)	3 (12%)	1.000
Follow-up time (within 1 month)	23.37 ± 10.78	24.92 ± 10.06	21.88 ± 11.44	0.400
Mortality at 1 month (ev/pm, ir%)**	17/38 (44.5%)	7/20 (35.1%)	10/18 (54.8%)	0.494[%]

*Mean ± standard deviation

[^]Median along with first and third quartiles

[#]*P* value from Mann–Whitney *U* test and Fisher exact test for continuous and categorical variables, respectively

**ev/pm: events/person months, ir%: incidence rate for 100-persons month

[§]*P* value from one-sample *t* test

[%]*P* value from Poisson regression model

Table 2 1-month mortality risk prediction and discriminatory power of MPI at admission, at discharge and procalcitonine (PCT) from univariate Cox regressions

Variable	Category	HR (95% CI)	*p* value	C-statistic (95% CI)
MPI at admission	–	1.38 (1.04–1.83)*	0.025	0.649 (0.532–0.766)
MPI at discharge	–	2.39 (1.48–3.87)*	<0.001	0.841 (0.745–0.937)
PCT (ng/mL)	At admission	1.00 (1.00–1.01)	0.051	0.630 (0.497–0.763)
	At 1 day	1.01 (1.00–1.03)	0.075	0.610 (0.468–0.752)
	At 3 days	1.03 (0.99–1.07)	0.156	0.673 (0.537–0.809)
	At 5 days	1.08 (0.99–1.18)	0.095	0.687 (0.551–0.823)

Risks were reported as hazard ratio (HR) along with their 95% confidence intervals (95%CI). Discrimination was reported as survival C-statistic along with their 95% CI

*Hazard ratio (*HR*) is referred for each increment of 0.1 MPI units

Table 3 Measures of discriminatory improvement and risk reclassification in predicting 1-month mortality for PCT, added to the model with MPI only

MPI variable	PTC variable	C-statistic for MPI (95% CI)	C-statistic for MPI + PTC (95% CI)	IDI* (95% CI)	*p* value for IDI
MPI at admission	At admission	0.649 (0.532–0.766)	0.688 (0.565–0.811)	0.045 (0.001, 0.126)	0.020
	At 1 day	0.649 (0.532–0.766)	0.693 (0.564–0.822)	0.065 (0.003, 0.142)	0.016
	At 3 days	0.633 (0.507–0.758)	0.675 (0.536–0.814)	0.053 (−0.005, 0.138)	0.049
	At 5 days	0.667 (0.534–0.799)	0.713 (0.575–0.851)	0.093 (0.002, 0.216)	0.017
MPI at discharge	At admission	0.841 (0.745–0.937)	0.843 (0.748–0.939)	−0.009 (−0.018, 0.002)	0.949
	At 1 day	0.841 (0.745–0.937)	0.848 (0.754–0.942)	−0.010 (−0.025, 0.007)	0.881
	At 3 days	0.847 (0.743–0.950)	0.842 (0.736–0.947)	0.000 (−0.007, 0.006)	0.497
	At 5 days	0.826 (0.714–0.939)	0.828 (0.713–0.942)	0.000 (−0.001, 0.001)	0.531

*Integrated discrimination improvement

patients with CAP. PCT levels also showed a prognostic power close to that of MPI performed at hospital admission, whereas PCT prognostic accuracy resulted significantly lower than the prognostic accuracy of MPI carried out at hospital discharge. PCT levels, however, may improve the prognostic accuracy for 1-month mortality of MPI at admission in hospitalized older patients with CAP.

PCT is a specific marker for the diagnosis of clinical relevant bacterial infections and sepsis even in the elderly population as confirmed by a recent meta-analysis [10]. Moreover, it has a double usefulness: while a basal value is helpful for distinguishing bacterial and non-bacterial infectious diseases, serial measurements of PCT can be used for the follow-up of severe bacterial infections to monitor the effectiveness of the therapeutic regimen in severe bacterial infection, since increasing PCT values may reflect continuing disease activity, while a decrease in PCT levels suggest the potential resolution of the infection [11]. Recently, many studies demonstrate a high prognostic value of PCT, alone or compared to some clinical scores (i.e., PSI and CURB 65), on short-term mortality in patients with CAP. Indeed, PCT, as a biomarker, was comparable to other clinical scoring systems for predicting mortality [12], while elevated PCT levels on hospital admission could help to identify patients who had an high mortality risk up to 28 days with a predictive value of PCT comparable to that of CURB-65 and more accurate than the measurements of CRP [13].

In our study, although PCT levels alone were slightly associated to 1-month mortality (95% confidence interval for hazard ratios almost cover the null value of the 1.00 in the univariable Cox analyses); however, PCT contributed to improve significantly the model's discrimination which originally included the MPI at admission (all IDI *p* values resulted statistically significant), but not the model's discrimination with MPI at discharge. A possible explanation could be that in the acute phase of disease, the prognosis is more influenced by the severity of the infection. Indeed, PCT levels reflect the intensity of the inflammatory response against the microorganism and the severity of infection. At discharge from hospital, exceeded the acute phase of the disease, the prognosis in the older patients is probably influenced either by the organ-specific failure, but also by the impairment of other domains, such as functional and cognitive disability, malnutrition, the presence of relevant comorbidities and multiple drug treatments, as well as co-habitation and psychosocial determinants [5]. There is now an agreement to suggest that all the domains

are better evaluated in the older people using a multidimensional approach using a CGA [14]. Indeed, a previous our study demonstrated that in elderly patients with CAP, the prognostic value of a CGA-based MPI was significantly higher than the prognostic tools such as PSI and Curb 65 in predicting short-term mortality [6]. These findings are in line with the conclusions of a recent review reporting that in the management of older patients with CAP, the treatment plan should take into account patients' wishes, but also functional, nutritional, and cognitive status as well as the severity of comorbidities and polytherapy [15].

The study has some limitations: it was an observational single-center study with a limited size of the sample; second, we did not include microbiological data; third, the severity of pneumonia was not taken into account; and finally, we did not collect the real cause of 1-month mortality.

In conclusion, in this population of hospitalized older patients with CAP, MPI significantly predicted 1-month mortality with higher prognostic accuracy when MPI was performed at discharge than at hospital admission. PCT serum levels may significantly improve the prognostic accuracy of MPI at admission. Further studies on larger populations are needed to better define the clinical usefulness of integrated multidimensional and biomarkers prognostic tools in the clinical decisions in older patients with CAP.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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