



RDW-based clinical score to predict long-term survival in community-acquired pneumonia: a European derivation and validation study

Remo Melchio¹ · Jacopo Davide Giamello¹ · Elisa Testa¹ · Luis Alberto Ruiz Iturriaga² · Andrea Falcetta¹ · Cristina Serraino¹ · Piero Riva³ · Christian Bracco¹ · Leyre Serrano Fernandez² · Salvatore D'Agnano¹ · Stefano Leccardi¹ · Massimo Porta³ · Luigi Maria Fenoglio¹

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Abstract

An excess long-term mortality has been observed in patients who were discharged after a community-acquired pneumonia (CAP), even after adjusting for age and comorbidities. We aimed to derive and validate a clinical score to predict long-term mortality in patients with CAP discharged from a general ward. In this retrospective observational study, we derived a clinical risk score from 315 CAP patients discharged from the Internal Medicine ward of Cuneo Hospital, Italy, in 2015–2016 (derivation cohort), which was validated in a cohort of 276 patients discharged from the pneumology service of the Barakaldo Hospital, Spain, from 2015 to 2017, and from two internal medicine wards at the Turin University and Cuneo Hospital, Italy, in 2017. The main outcome was the 18-month follow-up all-cause death. Cox multivariate analysis was used to identify the predictive variables and develop the clinical risk score in the derivation cohort, which we applied in the validation cohort. In the derivation cohort (median age: 79 years, 54% males, median CURB-65 = 2), 18-month mortality was 32%, and 18% in the validation cohort (median age 76 years, 55% males, median CURB-65 = 2). Cox multivariate analysis identified the red blood cell distribution width (RDW), temperature, altered mental status, and Charlson Comorbidity Index as independent predictors. The derived score showed good discrimination (c-index 0.76, 95% CI 0.70–0.81; and 0.83, 95% CI 0.78–0.87, in the derivation and validation cohort, respectively), and calibration. We derived and validated a simple clinical score including RDW, to predict long-term mortality in patients discharged for CAP from a general ward.

Keywords Community-acquired pneumonia · Prognosis · Red blood cell distribution width · Clinical score

Introduction

Community-acquired pneumonia (CAP) remain a major cause of morbidity and mortality worldwide [1]. Although early (e.g. in-hospital and 30-day mortality) is estimated to be 10% for patients admitted to a general ward [2], CAP has a strong impact on long-term prognosis (> 3 months). An increase in the death risk in CAP patients who were discharged from the hospital was as high as 50% in a 5-year follow-up, even after adjusting for age and comorbidities [3–5]. Thus, acute diseases such as pneumonia show an excess long-term mortality, comparable to that of the most common chronic conditions (e.g. cancer, heart failure). The ability to identify the patients at high risk of adverse outcome in an adequate timespan after the discharge from a medical ward for an episode of CAP remains challenging. Nevertheless, the availability of a bedside clinical prediction

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✉ Remo Melchio
remo.melchio@libero.it

¹ Department of Internal Medicine, A.O. S. Croce e Carle, Via Michele Coppino 26, 12100 Cuneo, CN, Italy

² Pneumology Service, Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain

³ Department of Medical Sciences, University of Turin - AOU Città della Salute e della Scienza di Torino, Turin, Italy

score could improve the home care management, follow-up organization and communication with patients and their relatives about prognosis.

A series of risk factors have been shown to be linked to long-term mortality in CAP, including elderly age, male sex, and chronic comorbidities [6, 7]. A well known and validated method for classifying comorbid conditions, the Charlson Comorbidity Index (CCI), when studied in CAP, has shown a poor accuracy as a standalone method for predicting 1-year mortality [8, 9]. Moreover, various biomarkers as pro-adrenomedullin, copeptin, endothelin-1, procalcitonin, and C-reactive protein have been associated with long-term prognosis [10–12]. Although some of these predictors are easy to obtain in clinical practice, others are more complex or expensive to acquire, limiting their widespread use at the bedside [13]. Red blood cell distribution width (RDW), a measure of anisocytosis, is a parameter that routinely reported in the complete blood cell counts, and, therefore, virtually available to all patients at no cost. Recently, several studies have evaluated its prognostic accuracy in various diseases [13–17], including pneumonia [18, 19]. Although high RDW values have been associated with unfavorable short and long-term prognosis in CAP, no multivariable model has been done so far.

Therefore, in this study, we used clinical and laboratory data (including RDW) from three European hospitals to derive and validate a risk prediction score, to estimate the 18-month mortality in patients who experienced an episode of CAP and were discharged from a general ward.

Methods

Study design and patients

We followed the TRIPOD [20] (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement for reporting multivariable prediction model development and validation. This study complied with the Declaration of Helsinki and was approved by the local ethics committees.

The derivation cohort consisted of all consecutive patients discharged from the Internal Medicine Department of the Santa Croce and Carle Hospital of Cuneo from 1 January 2015 through 31 December 2016 with a main diagnosis of ‘Community-Acquired Pneumonia’. The Cuneo Hospital is a tertiary 650-bed teaching hospital, with 25,000 admissions in 2016, located in the southern Piedmont region, Italy. We selected the patients by searching the administrative database of the hospital with the following discharge codes, according to the International Classification of the Diseases (ICD)-9: 480 to 487.0. Each retrieved patient record was

checked by JDG and CB to verify the inclusion and exclusion criteria.

Patients were diagnosed with CAP, if they had an acute illness with cough and at least one of new focal chest signs, fever > 4 days or dyspnoea/tachypnoea, without other obvious causes, supported by chest radiograph findings of the lung shadowing that were likely to be new, according to the European Respiratory Society Guidelines [21].

The exclusion criteria were (1) patients who died or were missing within the first 30 days of admission; (2) severe immunodepression (HIV infection, severe haematological diseases or immunosuppressive therapy); (3) leukopenia (< 1000 leukocyte per mm³) or neutropenia (< 500 neutrophils per mm³); (4) metastatic cancer; (5) pulmonary abscess or aspiration pneumonia; (6) possible nosocomial origin (< 30 days from hospital discharge); and (7) blood transfusion in the previous three months. In patients with multiple admissions, only the index admission was considered.

Patients were treated according to the guidelines of the European Respiratory Society (ERS) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) [21].

The derivation cohort included 315 patients (Supplemental Material Figure S1).

The external validation cohort was composed of 276 patients with CAP discharged in part from the Pneumology Service of the Hospital Universitario Cruces, Barakaldo in Bilbao, Spain from 2015 to 2017 ($n=96$) and in part from the Internal Medicine ward of the Città della Salute e della Scienza University Hospital of Turin (Italy) in 2016 ($n=114$), and from the Internal Medicine ward of the Santa Croce and Carle Hospital of Cuneo (Italy) in 2017 ($n=80$), (Supplemental Material Figure S1). The Spanish cohort is based on a prospective registry of consecutive immunocompetent adults (> 18 years) hospitalized for community-acquired pneumococcal pneumonia in Cruces Hospital [4]. For Italian cohort, inclusion and exclusion criteria were the same as in the derivation cohort.

Data collection

For each patient in the derivation cohort, demographic, clinical, laboratory, and radiological variables data were collected by consulting the records of the emergency departments, electronic medical records, and discharge summaries.

The variables collected included: demographic characteristics (sex and age), underlying diseases and comorbidities, residence in nursing home, dialysis, smoking, and home oxygen therapy. The Charlson Comorbidity Index, a weighted measure of comorbidities, was also calculated [9] (Supplemental Material, Figure S2).

Vital parameters, altered mental status (Abbreviated Mental Test < 8) [22] and laboratory data at admission were

also collected, glomerular filtration rate was estimated using the CKD-EPI formula [23]. RDW was reported as the coefficient of variation (in percent) of erythrocyte cell volume, and the blood count data were obtained using the Dasit Sysmex XE-5000 instrument. For each patient data on blood cultures, sputum, bronchoalveolar lavage (BAL), urinary legionella, and pneumococcal antigens were collected when available. Chest radiographs were examined to evaluate the bilateral involvement. Data on antibiotic therapy were also collected, reporting the class of drug used, the associations, and any changes in the treatment. Moreover, the Pneumonia Severity Index (PSI) [24] and CURB-65 [25], severity scores were calculated.

Study outcome

For both the derivation and validation cohorts, the main outcome was all-cause mortality at 18 months: this timespan was chosen for clinical convenience, and because it was evaluated in previous studies on CAP prognosis [11, 26]. Follow-up was performed by consulting the hospital information database connected to the Regional Registry Office or by phone calls to patients, to their relatives or to the referring primary physicians.

To assess the quality of follow up, we calculated the simplified person-time follow-up rate [27], which was 93% in the derivation cohort and 92% in the validation cohort.

Statistical analysis

Continuous variables with normal distribution are presented as mean \pm standard deviation, whereas those with non-normal distribution are presented as median and interquartile range. Categorical variables are presented as frequencies and percentages.

The sample size was calculated using the conservative rule of 10 events per candidate predictor: in the derivation cohort, 100 events allowed almost 10 candidate variables to be included in the multivariable Cox model. In the validation cohort, we needed almost 40 events to validate the 4-variables prediction model.

Survival curves were generated using the Kaplan–Meier method and compared with the log-rank test. In the derivation cohort, univariate and multivariate Cox proportional hazard models were used to identify the variables associated with survival. Only variables that reached a statistical significance ($p < 0.05$) in the univariate analysis were included in the full multivariate Cox models and were subjected to a stepwise multivariate Cox analysis.

We tested both a model with single comorbidities and age as covariates and a model with Charlson Comorbidity Index (a weighted score of comorbidities and age). Similarly, a model including PSI classes was evaluated along

with haemoglobin, RDW, eGFR, and C-reactive protein. The variables included in the final model after stepwise selection analysis were the Charlson Comorbidity Index, altered mental status, RDW, and temperature. Then, to estimate more easily the individual risk at the bedside, we generated a simplified score by dividing the β coefficients for each category by the smallest value of a β coefficient in the model to allocate an integer score for each variable [28]. The resulting derivative score was finally validated at the multicentre validation cohort.

As the simplification of the developed prediction model could have led to some loss of predictive accuracy, to assess the discriminatory power (i.e. the ability of the model to differentiate between those who do or do not experience the outcome event), we determined the area under the receiver-operating curve (AUC) for both the prediction model and the simplified final score in derivation and validation cohorts.

Model calibration (i.e. the agreement between predictions from the model and observed outcomes) was assessed by the calibration intercept and the calibration slope, and graphically by comparing observed (Kaplan–Meier) and predicted survival probabilities in three prognostic groups (low, medium, and high risk) derived by placing cut-points on the prognostic index [29, 30].

All tests were two-sided and statistical significance was accepted, if the P value was < 0.05 .

All statistical analyses were conducted using STATA/IC 14.0 software (StataCorp LP, USA).

Results

Derivation cohort

The clinical and laboratory characteristics of the derivation cohort are reported in Table 1.

The median age was 79 years, 54% were men, and the 18-month mortality rate was 32%. The main comorbidities were heart failure (19%), diabetes mellitus (20%), cerebrovascular disease (20%), non-metastatic cancer (20%), and COPD (18%). The median Charlson comorbidity index was 6 (IQR 4–8). The median value of CURB-65 was 2, and 66% of the population belonged to PSI class IV to V. The median RDW value at admission was 14.4% (95% CI 13.6–15.9). The most used antibiotics were beta-lactams and macrolides, administered to 62% of patients, followed by fluoroquinolones, administered to 37% of patients.

Validation cohort

The general characteristics of the validation cohort are shown in Table 1. Compared with the derivation cohort, patients were younger (median age: 76 years), had fewer

Table 1 Baseline characteristics of the derivation and validation cohorts

	Cohort, no. (%) of patients	
	Derivation (<i>N</i> = 315)	Validation (<i>N</i> = 276)
Demographics		
Age, median (IQR), years	79 (70–85)	76 (61–83)
Gender (women)	143 (45)	124 (45)
Nursing home resident	74 (23)	14 (5)
Comorbidities		
Coronary artery disease	40 (13)	34 (12)
Heart failure	59 (19)	33 (12)
Diabetes mellitus	64 (20)	61 (22)
Cerebrovascular disease	65 (20)	51 (18)
Dementia	38 (12)	25 (9)
COPD	58 (18)	54 (20)
Cancer	64 (20)	37 (13)
Chronic kidney disease (eGFR < 30)	42 (13)	24 (9)
Liver disease	15 (5)	9 (4)
Charlson Comorbidity Index	6 (4–8)	4 (2–6)
Number of comorbidities		
0	38 (12)	85 (30)
1	68 (21)	69 (25)
> 1	209 (66)	122 (44)
Active smoker	28 (18)	67 (24)
Severity of Pneumonia		
CURB-65 score	2 (1–2)	2 (1–2)
PSI score	102 (84–128)	93 (73–114)
PSI class I–II	39 (12)	70 (25)
III	66 (21)	72 (26)
IV	134 (42)	99 (36)
V	75 (24)	32 (12)
Vital parameters at admission		
Systolic blood pressure (mmHg)	133 ± 22	127 ± 23
Heart rate (bpm)	92 ± 18	94 ± 20
Respiratory rate (median, IQR)	16 (14–20)	20 (16–24)
Body temperature (median (IQR), °C)	37.7 (36.8–38.5)	37.3 (36.5–38.2)
Arterial oxygen saturation (%)	93 (90–96)	92 (88–95)
Altered mental status at admission (%)	67 (21)	35 (13)
Bilateral involvement at Rx (%)	65 (21)	65 (23)
Laboratory data		
Haemoglobin (g/L)	12.5 ± 1.9	12.7 ± 1.9
Haematocrit (median (IQR), %)	37.6 (34–41)	38.2 (35–42)
RDW (median (IQR), %)	14.4 (13.6–15.9)	14.2 (13.4–15.4)
eGFR (ml/min)	65.2 ± 28	67.9 ± 28
BUN (median (IQR), mg/dL)	23 (16–33)	22 (15–32)
C-Reactive Protein (median (IQR), mg/dL)	68 (33–191)	43 (21–125)
Procalcitonin (mg/L)	0.27 (0.12–1.3)	0.20 (0.1–1.0)*
Sodium (mEq/L)	138.3 (135–141)	137 (134–139)
Glucose (mg/dL)	128 (109–152)	130 (107–163)
Primary outcome		
18-month mortality	102 (32)	51 (18)

Data are expressed as number (percentage), mean ± standard deviation or median (25–75% percentiles) as appropriate

BUN blood urea nitrogen, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *PSI* Pneumonia Severity Index, *RDW* red cell distribution width

*Data available for *N* = 187

comorbidities (55% had 1 or no comorbidities), and belonged to a PSI class IV or V in 48% of cases. The median CURB-65 score was 2, similar to that of the derivation cohort. The median RDW value at admission was 14.2% (95% CI 13.4–15.4) (Table 1). The 18-month mortality rate was 18% (51 patients). Based on the available data, the most used antibiotics were beta-lactams and macrolides, administered to 77% of the patients, followed by fluoroquinolones, administered to 22% of patients.

Univariate analysis

The univariate analysis of the derivation cohort (Table 2), identified the variables associated with the main outcome. For each year increase in age, the risk of death increased by 3% (95% CI 1–5%). Among the comorbidities, heart failure, dementia, chronic kidney disease, and chronic liver disease were associated with an increased risk of 18-month mortality. For every point increase of the Charlson Comorbidity Index, the incremental mortality risk was 21%. In patients presenting in the ED with altered mental status, the risk of death at 18 months tripled (HR 3.2, 95% CI 2.1–4.8), increased body temperature was associated with reduced mortality by 25% for each additional degree (HR 0.75, 95% CI 0.62–0.92). Among the laboratory variables, haemoglobin, RDW, eGFR, BUN, and C-reactive protein were associated with the survival. Specifically, for every additional percentage increase in RDW value at the admission, 18-month mortality increased by 18% (95% CI 9–28%) and an RDW greater than or equal to the median value (14.4%) almost doubles the probability of death during follow-up (HR 1.89, 95% CI 1.39–2.56). The severity of pneumonia, assessed by the CURB-65 score or PSI classes, was also strongly associated with the long-term survival.

Multivariate analysis and score validation

Variables that reached statistical significance ($p < 0.05$) in the univariate analysis were included in the full multivariate Cox model and were subjected to a stepwise multivariate Cox regression analysis. To avoid duplicate covariate insertion, we tested both a model with single comorbidities and age as covariates and a model with the Charlson Comorbidity Index (a weighted score of comorbidities and age). For the same reason, a model including PSI classes was evaluated along with haemoglobin, RDW, eGFR, and C-reactive protein.

The variables included in the final Cox model after stepwise selection analysis were the Charlson Comorbidity Index, altered mental status, RDW, and temperature (Table 3, Model 2).

Discrimination was evaluated by calculating the area under the receiver operating curve (AUC) of the

Table 2 Univariate analysis of risk factors associated with 18-month mortality in the derivation cohort ($N=315$)

	HR	95% CI	<i>p</i> value
Demographics			
Age, years	1.03	1.01–1.05	0.005
Gender (women)	0.97	0.65–1.44	0.87
Nursing home resident	1.35	0.87–2.10	0.17
Comorbidities			
Coronary artery disease	1.33	0.76–2.30	0.30
Heart failure	1.91	1.23–2.96	0.004
Diabetes mellitus	1.15	0.72–1.85	0.54
Cerebrovascular disease	1.03	0.64–1.67	0.90
Dementia	2.97	1.87–4.71	0.000
COPD	1.14	0.70–1.85	0.57
Cancer	1.38	0.88–2.16	0.15
Chronic kidney disease	1.21	0.99–1.47	0.06
Liver disease	1.59	1.21–2.08	0.001
Charlson comorbidity score	1.21	1.11–1.32	0.000
Active smoker	1.35	0.67–2.73	0.85
Severity of pneumonia			
CURB-65	1.86	1.42–2.41	0.000
PSI class	1.77	1.40–2.25	0.000
Vital parameters at admission			
Systolic blood pressure (mmHg)	0.99	0.99–1.00	0.94
Heart rate (bpm)	1.00	0.99–1.01	0.10
Respiratory rate	1.04	0.99–1.09	0.08
Body temperature (°C)	0.75	0.62–0.92	0.006
Arterial oxygen saturation (%)	0.98	0.93–1.02	0.25
Altered mental status at admission (%)	3.23	2.16–4.82	0.000
Bilateral involvement at Rx (%)	1.03	0.65–1.65	0.88
Laboratory data at admission			
Haemoglobin (g/L)	0.85	0.77–0.95	0.006
Haematocrit (%)	0.98	0.95–1.03	0.42
RDW (%)	1.18	1.09–1.28	0.000
eGFR (ml/min)	0.991	0.984–0.998	0.01
BUN (mg/dL)	1.02	1.01–1.03	0.000
C-reactive protein (mg/dL)	0.997	0.996–0.999	0.03
Procalcitonin (mg/L)	0.984	0.951–1.017	0.34
Sodium (mEq/L)	1.02	0.99–1.05	0.15
Glucose (mg/dL)	1.00	0.99–1.00	0.32

Data are expressed as Number (Percentage), mean \pm standard deviation or median (25–75% percentiles) as appropriate

BUN Blood Urea Nitrogen, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *PSI* Pneumonia Severity Index, *RDW* red cell distribution width

*Data available for $N=283$

prediction model in the derivation (c-statistic 0.77, 95% CI 0.72–0.82) and validation cohorts (c-statistic 0.85, 95% CI 0.80–0.89) (Fig. 1). Model calibration was assessed by the calibration intercept and the calibration slope, and

Table 3 Cox multivariable models for prediction of 18-month mortality in the derivation cohort ($n = 315$)

	Variable	Beta	HR	95% CI	<i>p</i> value
Model 1	Heart failure (yes/no)	0.69	2.00	1.25–3.18	0.003
	CKD (yes/no)	0.65	1.91	1.12–3.30	0.01
	Liver disease (yes/no)	1.24	3.47	1.64–7.37	0.001
	Dementia	0.68	1.98	1.14–3.44	0.01
	Altered mental status (yes/no)	0.92	2.51	1.54–4.09	0.000
	RDW (%)	0.17	1.19	1.08–1.30	0.000
	Temperature (°C)	−0.23	0.79	0.65–0.96	0.02
Model 2	Charlson Comorbidity Index (every 1 point)	0.18	1.19	1.09–1.31	0.000
	Altered mental status (yes/no)	1.04	2.83	1.87–4.27	0.000
	RDW (%)	0.15	1.17	1.07–1.27	0.001
	Temperature (°C)	−0.20	0.81	0.67–0.99	0.04
Model 3	PSI class (every 1 class, I to V)	0.61	1.85	1.42–2.40	0.000
	RDW (%)	0.17	1.18	1.08–1.30	0.000
	Temperature (°C)	−0.27	0.76	0.63–0.92	0.006

CKD chronic kidney disease, PSI Pneumonia Severity Index; RDW red cell distribution width

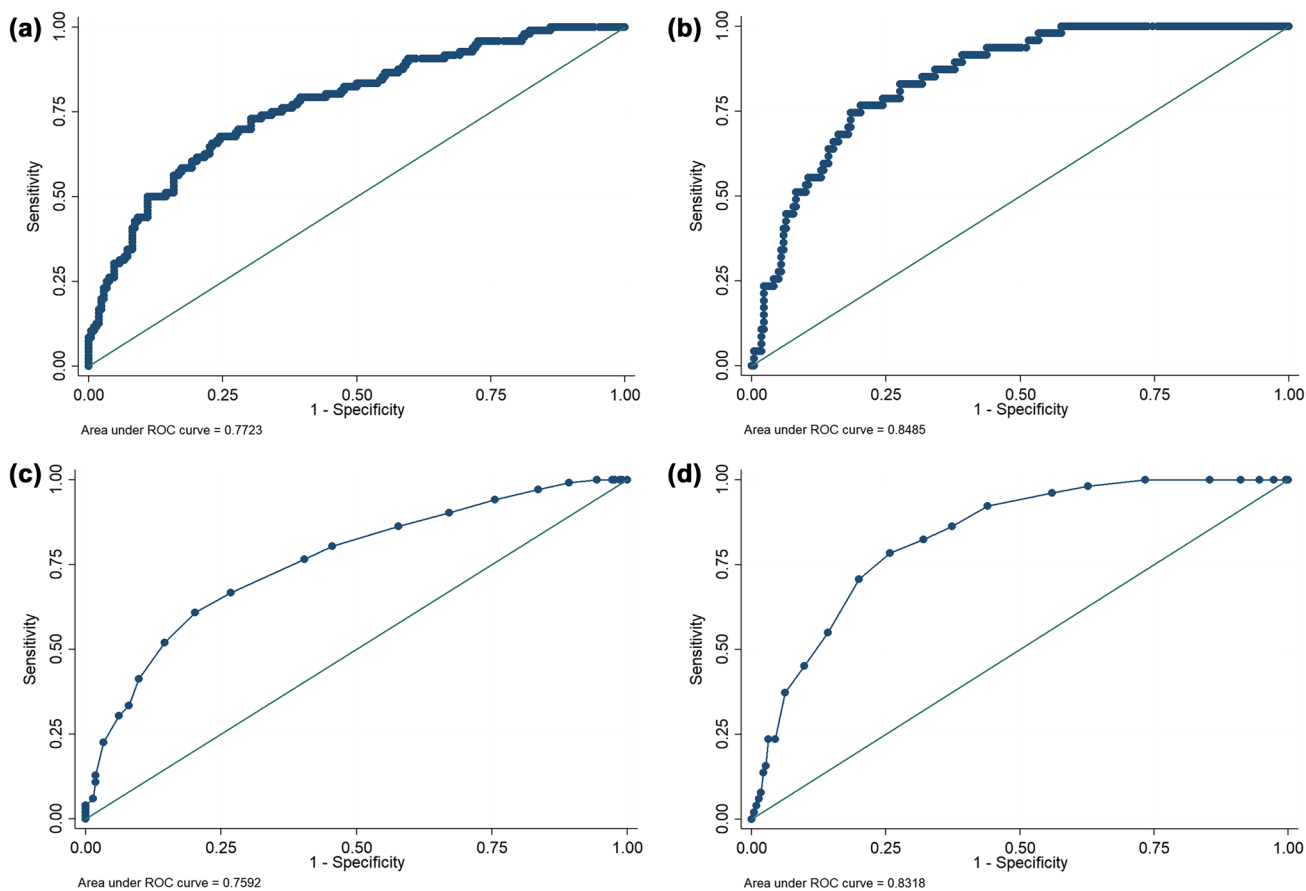


Fig. 1 Performance (c-statistic) of the final model and the simplified score. Top: AUC of the final model in the derivation (a) and validation (b) cohorts. Bottom: AUC of the score in the derivation (c) and validation (d) cohorts

graphically by comparing observed (Kaplan–Meier) and predicted survival probabilities in three prognostic groups (low, medium, and high risk) derived by placing cut-points on the 25th and 75th percentile of the prognostic index (Fig. 2). We then divided the β coefficients for each category by the smallest value of a β coefficient in the derivation model, to allocate an integer score for each variable (Table 4). The resulting derivative score was finally validated in the external validation cohort, and measures of discrimination and calibration were calculated accordingly (Figs. 1, 2, and 3). The score showed an overall good accuracy as expressed by the c-statistic = 0.83 (95% CI 0.78–0.87) and by the calibration slope = 1.09 (Fig. 3). Adding RDW significantly improved the prediction score in the derivation (AUC = 0.67, 95% CI 0.60–0.73, without RDW; vs AUC = 0.76, 95% CI 0.70–0.81, with RDW; $p = 0.001$) and in the validation cohort (AUC = 0.78, 95% CI 0.72–0.84, without RDW; vs AUC = 0.83, 95% CI 0.78–0.87, with RDW; $p = 0.05$; Supplemental Material, Figure S3).

Discussion

In this study involving more than 500 patients who were discharged after an episode of CAP from three European hospitals, we derived and validated a simple risk-prediction score to estimate the risk of 18-month mortality.

The predictors that were included in the final multivariate model and used to compose the score were age and comorbidities (summarized and weighted in the Charlson Comorbidity Index), altered mental status, temperature, and RDW at admission.

Several studies have assessed the association between comorbidities, age, biomarkers, severity of pneumonia, and long-term mortality in patients with CAP [4–8, 10, 11].

Guerter et al. in a derivation study including 877 patients with CAP, enrolled in the multicenter ProHOSP trial showed that male sex, age, comorbidities (COPD and cancer), low temperature, low CRP and high pro-adrenomedullin values were all independently associated with 18-month mortality [11]. Although the derived score has not yet been validated,

Fig. 2 Kaplan–Meier estimated the event-free survival rates per risk stratum in the derivation (a) and validation (b) cohorts. Observed and predicted survival probabilities in three prognostic groups (low, medium and high risk) were derived by placing the cut points on the 25th and 75th percentiles of the prognostic index

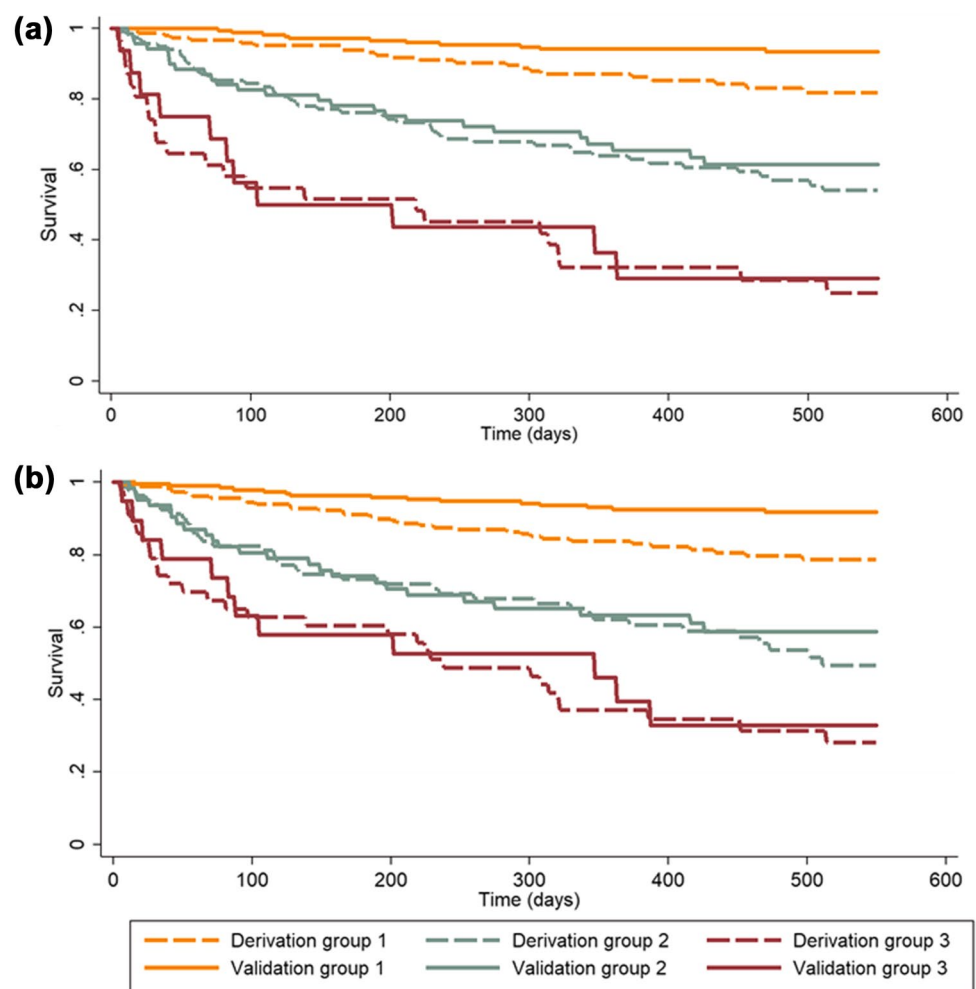


Table 4 18-month mortality risk index for patients with CAP

RDW (%)	Points
12–13	0
13–14	1
14–15	2
15–16	3
16–17	4
17–18	5
18–19	6
19–	7
Temperature (°C)	Points
<35	5
35–35.9	4
36–36.9	3
37–37.9	2
38–38.9	1
39–	0
Altered mental status	Points
Yes	6
No	0
Charlson Comorbidity Index	Points
Total risk score	=()

Point values for each variable (A patient's total risk score can be obtained by summing points assigned to values of each variable, which can determine his/her corresponding predicted 18-month mortality risk)

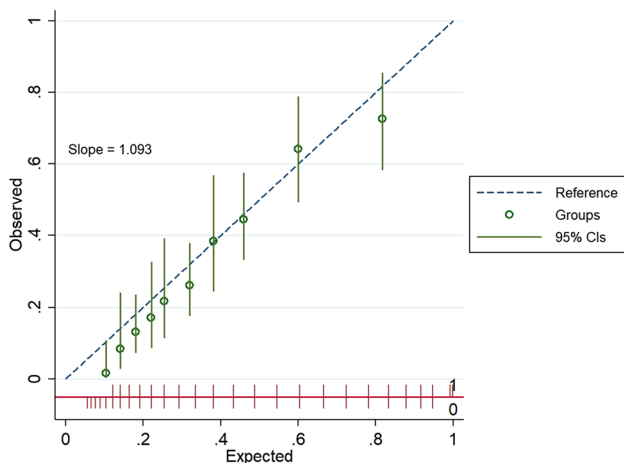


Fig. 3 Calibration plot comparing 18-month mortality risk in derivation and validation cohorts for patients discharged from a general ward after an admission for CAP

several variables, including comorbidities, age, and low temperature are also present in our model. Our study confirms the association between low temperature, CRP values, and worse outcome, a finding possibly ascribed to a reduced immune and inflammatory response in the elderly

population. Age-associated alterations in immune surveillance and dysfunctional immune response regulation can be responsible for increased susceptibility to infectious stimuli, and hence, a poor prognosis [31, 32]. Moreover, as expected in our older population, a model including single comorbidities and age or including the Charlson Comorbidity Index, showed a similar prognostic accuracy in the derivation cohort.

In addition, the results of our study confirm the strong ability of RDW in predicting long-term mortality in patients who were discharged for CAP from a general ward: an RDW > 14.4% (the median value of our population) almost doubles the probability of death at 18 months. Moreover, our data confirm the previous findings showing that its prognostic value is independent of haemoglobin values and comorbidities [13]. Furthermore, our analysis showed a significant improvement in the prediction accuracy when RDW was added to the clinical score, as assessed by comparing the AUCs when calculated with or without this covariate in both the cohorts. Several studies have associated RDW with short-term outcomes in CAP, such as complicated hospitalization, intra-hospital mortality, 30-day mortality and the need to switch to intensive care [33–35]. Torres first studied RDW (comparing it with pro-adrenomedullin) on

longer-lasting follow-up, showing a good long-term predictive power in CAP [18], as our data confirms.

The pathophysiological mechanism linking RDW with mortality is not yet understood. It has been suggested that anisocytosis could be a marker of cellular aging, inflammation, oxidative stress, hypoxia, splenic immune dysregulation or poor nutritional status, all associated with erythropoiesis or hemocathesis abnormalities [16, 36]. However, a high RDW could also contribute to a worse prognosis, because less deformable erythrocytes could impair tissue oxygenation [14]. Moreover, Corrales et al. have suggested an increased risk of cardiovascular disease during and after serious infections, such as pneumonia, and it is suggested that cardiovascular events may play an important role in long-term outcomes [37, 38]. Since RDW has been associated with cardiovascular mortality in patients with and without pre-existing heart diseases [39, 40], one could speculate that our multivariable prediction model could have intercepted a portion of the outcome linked to cardiovascular death.

As in the derivation cohort the 23% of patients were nursing home residents, one could argue that the inclusion of nursing home-acquired pneumonia, a subset of the health-care-associated pneumonia (HCAP), could have affected our results. However, it is debated whether to consider HCAP, as a distinct clinical entity in Europe [41]. As summarized in the International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia, studies in the USA have reported that HCAP is often caused by multidrug-resistant microorganisms in critically ill patients. In contrast, European data [42] suggest that the aetiology in HCAP patients is similar to that of CAP and that these patients are often not critically ill [43]. In addition, some authors suggest that comorbidities, dementia, aspiration pneumonia, functional impairment and recurrent hospitalization, are probably more significant issues in predicting long-term prognosis for patients with pneumonia acquired in a nursing home [41]. In our study we addressed these variables, excluding patients with aspiration pneumonia, and recurrent hospitalization, and including the comorbidities in the final model. This patient selection method could explain the lack of association of the category ‘nursing home residents’ with mortality in the univariate analysis in our study.

To confirm this hypothesis, we performed a secondary analysis in the derivation cohort after removing the nursing home residents from the analysis (Supplemental Material Table S1). In this new population ($N=241$, median age: 75 years, 25–75 percentile 70–84), 18-month mortality was 30%, and univariate analysis confirmed the associations observed in the primary analysis. Multivariate analysis showed that RDW, altered mental status, and

Charlson comorbidity index all maintained the predictive value found in the primary analysis, however, the temperature did not, probably because of the reduced sample size.

Furthermore, the external validation cohort displayed a lower burden of comorbidities, and therefore, as expected, showed a lower mortality rate, compared with the derivation cohort. Despite these important differences, the derived score showed good predictive power, as shown by a good discrimination (accuracy) and calibration (accuracy across a range of predicted probabilities) in the validation cohort.

Finally, the risk score has important characteristics for clinical practice. It is based on the readily available clinical and laboratory values, and provides estimates of long-term mortality, offering clinicians caring for patients with CAP as a simple tool to select high-risk patients, organize follow-up, and eventually, communicate with patients and their relatives about prognosis.

We acknowledge that our study has several limitations. First, it was a retrospective observational study, and derivation analysis was based on data collected in a single institution. However, the variables used in the final model (including RDW) were available in all patients included in the study, avoiding potential selection bias due to an incomplete collection of data typical of a retrospective design. Second, although the prognostic model shows good accuracy in the discrimination and calibration analysis, we are aware that residual confounding could be present. Third, an analysis of cause-specific mortality could not be performed because the causes of death at long-term follow-up could not be consistently identified. Fourth, observational and registry data show that the hospital admission is associated with an increased prevalence of drug interactions and polypharmacy (the use of five or more prescribed drugs at the same time) in older patients, with potential negative prognostic effects [44, 45]. Although polypharmacy could be an appealing variable to be included in a prognostic model for an elderly population with a high comorbidity index, this data is lacking for most of our patients. However, to date, the association between polypharmacy and long-term mortality in CAP has not yet been established.

In conclusion, we derived and validated a clinical score to predict 18-month mortality in patients who survived after an acute episode of CAP. For the first time, we introduced RDW in a multivariable predictive model including age, comorbidities, altered mental status and temperature at admission. Further studies are needed to evaluate the clinical impact of the score on the follow-up of patients with CAP discharged from a general ward.

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Compliance with ethical standards

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

Ethics 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. The study was approved by the institutional ethic committee.

Consent to participate This is a retrospective study that includes anonymized patients extracted from the hospital database, data are presented aggregated and anonymously. No informed consent was taken.

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