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Original article

Validation of the BAP-65 score for prediction of in-hospital death or use of mechanical ventilation in patients presenting to the emergency department with an acute exacerbation of COPD: a retrospective multi-center study from the Italian Society of Emergency Medicine (SIMEU)

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ABSTRACT

Exacerbations of chronic obstructive pulmonary disease (COPDE) frequently require hospitalizations, may necessitate of invasive mechanical ventilation (IMV), and are associated with a remarkable in-hospital mortality. The BAP-65 score is a risk assessment model (RAM) based on simple variables, that has been proposed for the prediction of these adverse outcomes in patients with COPDE. If showed to be accurate, the BAP-65 RAM might be used to guide the patients management, in terms of destination and treatment. We conducted a retrospective, multicentre, chart-review study, on patients attending the ED for a COPDE during 2014. The aim of the study was the validation of the BAP-65 RAM for the prediction of in-hospital death or use of IMV (composite primary outcome). We assessed the discrimination and the prognostic performance of the BAP-65 RAM. We enrolled 2908 patients from 20 centres across Italy. The mean (standard deviation) age was 76 (11) years, and 38% of patients were female. The composite outcome occurred in 5.3% of patients. The AUROC of BAP-65 for the composite outcome was 0.64 (95%CI 0.59–0.68). The sensitivity of BAP-65 score ≥ 4 to predict in-hospital mortality was 44% (95% CI 34%–55%), the specificity was 84% (95% CI 82%–85%), the positive predictive value was 9% (95% CI 6%–12%), and the negative predictive value was 98% (95% CI 97%–98%).
Conclusions: In patients attending Italian EDs with a COPDE, we found that the BAP-65 score did not have sufficient accuracy to stratify patients upon their risk of severe in-hospital outcomes.

1. Introduction

1.1. Background and rationale

"Chronic Obstructive Pulmonary Disease (COPD) is defined as a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases." in the 2017 report from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1] Patients with COPD often experience exacerbations (COPDE), defined as "acute worsening of respiratory symptoms that result in additional therapy" [1]. The spectrum of clinical presentation of COPDEs is wide: in some case they can be treated at home, but they often induce the patients to access the emergency department (ED), and might require hospitalization. In severe cases, invasive mechanical ventilation (IMV) is necessary, and the incidence of in-hospital mortality is not negligible [2]. We recently conducted a research project under the auspices of the Italian Society of Emergency Medicine (SIMEU), aimed at collecting epidemiological data on patients accessing 34 Italian EDs with a suspect of COPDE [3]. In summary, we found these patients to have a mean age of 77 years and to experience an important burden of comorbidity. The admission rate was 65%, and the estimated cost per patient was € 2617. The use of a risk assessment model (RAM) to predict patients prognosis and therefore guide decisions on the patients' destination (discharge, short-term observation, hospital medical ward or intensive care), and on type and intensity of monitoring, treatment and follow up during and after the acute episode can represent a step toward the improvement of the efficiency of care for COPDE in the ED. Among several RAMs proposed for patients with COPDE, the BAP-65 [4] is based on information which is easily available (elevated blood urea nitrogen [BUN], altered mental status, pulse > 109 beats/min, age > 65 years) and may serve emergency clinicians as a simple and rapid risk-stratification tool. The BAP-65 RAM has been derived and validated in cohorts of inpatients, admitted for COPDE in the United States (US). In these patients, the BAP-65 RAM showed a good accuracy for the

prediction of the risk of mortality and the use of IMV during the hospital stay [4,5]. In particular, in the derivation and internal validation study, Tabak and colleagues [4] found an AUROC for mortality of 0.72 (95% confidence interval [CI], 0.70–0.74) in the derivation and 0.71 (95% CI, 0.70–0.73) in the internal validation cohort, respectively. The AUROC for IMV was 0.77 (95% CI, 0.75–0.79) for both the cohorts. The same research group, further validated the model with data from the same database on a different time period [5], estimating an AUROC of 0.77 (95% CI, 0.76–0.78) for mortality, of 0.78 (95% CI, 0.78–0.79) for the use of IMV, and of 0.79 (95% CI, 0.78–0.80) for the composite outcome death and IMV.

However, to the best of our knowledge, the BAP-65 RAM has never been validated in the ED setting, where it could help to make decisions about the intensity of care and destination based on patient risk. Moreover, it has never been validated in Europe. If showed to be accurate for the prediction of poor prognosis in an ED population, the BAP-65 RAM could help the physicians in the management of patients with COPDE.

1.2. Objectives

The present study aimed at the validation of the BAP-65 RAM for the prediction of in-hospital mortality and/or the use of IMV in an Italian cohort of patients attending the ED for an COPDE. This was a pre-specified objective of the above-mentioned COPD-SIMEU research project [3]. Secondary objectives were the prediction of in-hospital mortality, use of IMV or or non-invasive mechanical ventilation (NIV), separately.

2. Material and methods

2.1. Study design

This was a retrospective cohort, multicentre, validation study. The present manuscript has been prepared according to the RECORD [6] and the TRIPOD [7] statements.

2.2. Study population and data collection

The study population, with inclusion and exclusion criteria, is described in detail in a previous manuscript [3]. In brief, patients aged > 40 years attending the ED of one of the included centres during 2014 and discharged from the ED (to the ward, ICU or home) with a diagnosis of COPDE were eligible. The EDs databases were used for patients' selection and for data extraction. The diagnosis of COPDE was based on the International Classification of Diseases, 9th Revision (ICD9) code 491.21 or on the textual diagnosis, and further confirmed checking the data in the clinical chart. The researchers of each participating centre manually reviewed the charts to extract the data, following a detailed data extraction manual created ad hoc. FG, GV, and DA centrally reviewed the data quality and, when needed, local investigators were contacted for clarifications.

2.3. Outcomes

The primary outcome of the study was the composite of in-hospital death and the use of IMV.

Secondary outcomes were separately the occurrence of in-hospital death the use of IMV, and the use of NIV.

2.4. Predictors

The BAP-65 RAM refers to information available on initial hospital presentation. The three main variables are BUN level > 25 mg/dL, altered mental status, and pulse > 109 beats/min. Patients who have none of these risk factors and are aged < 65 are designated as class I, while patients with no risk factors who are aged 65 years or more are classified as class II. Patients who have one, two, or three main risk factors are designated into risk classes III, IV, and V, respectively. The occurrence of altered mental status was defined as a Glasgow Coma Score < 14 or a description by the physician of disorientation, stupor, or coma [4].

As possible pre-specified confounders, we recorded information regarding sex, blood pressure at presentation, the presence of pneumonia or respiratory failure, and the variables included in the Charlson Comorbidity Index (CCI) [8]. Respiratory failure was defined as SpO2 < 90% presence of respiratory failure among the discharge.

Respect to the derivation study [4], the population of this study differed for the setting, as we enrolled patients presenting to the ED for an COPDE either being admitted or discharged, while the derivation cohort was only composed of hospitalized patients. Besides that, eligibility criteria, outcome, and predictors of the validation cohort matched the derivation study.

2.5. Ethical considerations

The research was conducted according to the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee. A waiver for informed consent was obtained, given the retrospective nature of the study and the fact that data were anonymized before being entered in the general database.

2.6. Analysis

The baseline characteristics of the population were tabulated using standard descriptors of central tendency and variability (mean and standard deviation [SD] or ranges, as appropriate). We assessed the association between the BAP-65 score, other pre-specified variables, and the composite outcome using logistic regression, both univariate and multivariable, considering the centers as clusters. We included in the multivariable analysis the variables that showed a statistically significant association with the composite outcome at the univariate analysis. The calibration of the risk score predictions was evaluated by plotting observed proportions versus predicted probabilities and by calculating the calibration slope and intercept [7]. The AUROC was used to assess the model's discrimination. Moreover, we derived sensitivity, specificity, positive predictive value, and negative predictive value of a BAP-65 ≥ 4 for the primary outcome. The AUROC, sensitivity, specificity, positive and negative predictive values were calculated also for the secondary outcomes. As a sensitivity analysis, we conducted the same analyses excluding patients with Pneumonia. The rationale for this sensitivity analysis is that some studies and recent guidelines exclude pneumonia when defining a COPD exacerbation [1,9].

2.6.1. Sample size

The composite outcome was expected to occur in at least 5% of the study population [5,10,11]. We estimated a sample size of 2000 patients, since 100 patients with the outcome of interest have been suggested for validation studies to be able to reliably detect different types of model invalidity [12].

2.6.2. Missing data

In some centres participating in the COPD-SIMEU project, the study collaborators were not able to retrieve data concerning the outcome or the variables included in the BAP-65 RAM. If the percentage of missing data for one of these variables was > than 25%, we decided to exclude the centre from the present analysis. We compared the characteristics of these two groups (included and excluded patients) using the *t*-test for continuous variables and either the Pearson's chi-squared or the Fisher's exact test for proportions, as appropriate. For the remaining centres, we assumed missing data occurred at random and performed multiple

imputations using the chained equations method, creating twenty different imputed data sets [13].

3. Results

The BAP-65 score was calculated on 2908 patients from 20 centres. Other 14 centres (1488 patients) were not able to provide the data required for the calculation of BAP-65 score (i.e. missing data for one or more variable were > 25%) and were excluded from the analysis. The most commonly missing data was urea, not measured in 1244 of the 1488 patients (84%). Table 1 shows the characteristics of the study population. The mean (SD) age was 76 years and 38% were female. A comparison with the characteristic of the patients excluded from this analysis is shown in eTable 1. In the validation cohort, data on the calculation of the BAP-65 score were missing in 10.7% of the cases. For all the other predictive and outcome variables, missing data were lower than 5% (see eTable 2). Table 2 shows a comparison of the distribution of demographics, predictors and outcomes among the derivation [4] and validation cohorts. Patients' distribution and outcomes frequencies among the 5 BAP-65 classes are reported in Table 3. Table 4 shows the unadjusted and adjusted association between each candidate predictor and outcome. The distribution of each predictor according to the occurrence of the composite outcome is shown in eTable 3. The multivariable analysis showed a statistically significant association ($p < 0.05$) between BAP-65 score (OR 1.74, 95% CI 1.29–2.11) and hypotension (3.12, 95% CI 1.21–8.00), and the composite outcome.

The calibration plot for the composite outcome is shown in Fig. 1 (slope = 0.69, intercept 1.7). Fig. 2 shows the ROC curve of BAP-65 for the composite outcome. The AUROC was 0.64 (95% CI 0.59–0.68). The sensitivity of BAP-65 score ≥ 4 to predict the composite outcome was 40% (95% CI 32%–49%), the specificity was 84% (95% CI 82%–85%), the positive predictive value was 12% (95% CI 9%–15%), and the negative predictive value was 96% (95% CI 96%–97%).

For the outcome in-hospital mortality, the AUROC for BAP-65 was 0.66 (95% CI 0.60–0.71). The sensitivity of BAP-65 score ≥ 4 to predict in-hospital mortality was 44% (95% CI 34%–55%), the specificity was 84% (95% CI 82%–85%), the positive predictive value was 9% (95% CI 6%–12%), and the negative predictive value was 98% (95% CI 97%–98%).

The AUROC for BAP-65 was 0.61 (95% CI 0.54–0.69) for IMV. The sensitivity of a BAP-65 score ≥ 4 to predict the use of IMV was 36% (95% CI 23%–52%), the specificity was 83% (95% CI 82%–85%), the positive predictive value was 4% (95% CI 2%–6%), and the negative predictive value was 99% (95% CI 98%–99%).

At the sensitivity analysis conducted excluding patients with pneumonia (2242 patients analysed), the AUROC for the BAP-65 score was 0.64 (95% CI 0.59–0.70) for the composite outcome. The sensitivity of a BAP-65 score ≥ 4 to predict the composite outcome was 42% (95% CI 32%–52%), the specificity was 85% (95% CI 83%-86%), the positive predictive value was 12% (95% CI 9%–16%), and the negative predictive value was 97% (96% CI 96%–97%).

4. Discussion

We assessed the accuracy of the BAP-65 score for the prediction of adverse outcomes on over two-thousand and nine-hundred patients. The AUROC of the BAP-65 RAM for the composite outcome (in-hospital mortality and/or use of IMV) was 0.64 (95% CI 0.59–0.68), with a sensitivity of 40% and a specificity of 84%. The AUROC for mortality was 0.66 (95% CI 0.60–0.71) and the AUROC for the use of IMV was 0.61 (95% CI 0.54–0.69). These results did not meaningfully change when patients with pneumonia were removed from the analysis. To our knowledge, this is the first attempt of validation of the BAP-65 RAM in the ED setting and the first one in general in a European cohort. We believe that this is important, because the model has been derived in an inpatient setting, while it is mainly meant to be used in the ED. It would not be appropriate to use the model in a setting different from the one in which it has been derived, without a new validation. Moreover, it is common in clinical research not to assume generalizability across populations differing for geographical, ethnical, and socio-cultural reasons, and across health systems. In particular, in this specific case, it is reasonable to think that the differences in the health system between US and Italy could affect the case mix of patients accessing ED with COPDE in terms of severity of the index disease and comorbidities, and physicians' behaviours (e.g. attitude to use IMV) [14,15]. Another strength of the study is the large number of contributing centres, which

Table 1
Characteristics of patients with exacerbation of chronic obstructive pulmonary disease seen in the emergency department.

Characteristic	BAP-65 validation cohort (n = 2908, 20 centres) N. (%)/mean (SD)
Demographics	
Female	1112 (38.2)
Age, years	76.2 (10.7)
CCI	
Class 1 (CCI 0)	789 (27.1)
Class 2 (CCI 1-2)	1230 (42.3)
Class 3 (CCI 3-4)	593 (20.4)
Class 4 (CCI ≥ 5)	296 (10.2)
Current respiratory medications	
Oxygen therapy	694 (24.7)
Inhaled beta agonists	1403 (50.8)
Inhaled anticholinergic	933 (33.8)
Inhaled steroid	1226 (44.4)
Systemic steroids	491 (17.8)
Theophylline	205 (7.4)
Antibiotics	409 (14.7)
Non-invasive ventilation (NIV)	79 (2.8)
CPAP	64 (2.3)
Arrival status	
Ambulance call	1552 (53.6)
Tachycardia (> 109 bpm)	492 (17.7)
Tachypnea (> 20)	1177 (47.4)
Systolic blood pressure < 90 mmHg	36 (1.3)
Sat02 < 90%	747 (26.2)
ED therapy	
Oxygen therapy	1701 (58.9)
Bronchodilators	1652 (57.3)
Inhaled beta agonists	1617 (56.1)
Inhaled anticholinergic	1035 (36.0)
Steroids	2003 (69.5)
Inhaled steroids	1546 (53.7)
Systemic steroids	1451 (50.4)
Both inhaled and systemic	994 (32.8)
Systemic beta agonists	15 (0.5)
Theophylline	169 (5.8)
Antibiotics	708 (24.5)
Non-invasive ventilation (NIV)	200 (6.9)
CPAP	68 (2.4)
Associated conditions	
Respiratory failure	918 (31.7)
Pneumonia	333 (11.5)
Altered mental status	227 (8.0)
ED disposition	
Discharged	764 (26.3)
Short-term observation	53 (1.8)
Admitted to hospital	1913 (65.8)
Others	177 (6.1)
Department of admittance	
Critical care	27 (1.6)
Internal Medicine & Geriatrics	1337 (80.9)
Pulmonology	254 (15.4)
Others	34 (2.1)
Outcomes	151 (5.3)
Mechanical ventilation	55 (1.9)
In hospital death	110 (3.8)

SD: standard deviation, ED: Emergency Department, CPAP: Continuous Positive Airway Pressure.

Table 2
Comparison of the BAP-65 derivation and validation cohorts.

Characteristics of patients	Validation cohort (present study), N. (%) (n = 2908, 20 centres)	Derivation cohort [4], N. (%) (*n* = 43,893, 191 centres)
Demographics		
Female	1112 (38.2)	24,047 (54.8)
Age, years	78 (70–84)*	72 (63–79)*
BAP items		
Blood urea > 25	1948 (70.7)	8564 (19.5)
Age > 65	2459 (84.6)	NA
Pulse > 109 beats/min	492 (17.7)	13,063 (29.8)
Altered mental status	227 (8.0)	3493 (8.0)
Outcomes		
Invasive mechanical ventilation	55 (1.9)	926 (2.1)
In hospital death	110 (3.8)	774 (1.8)

NA: not available.
* Median (1st and 3rd quartile).

Table 3
Distribution of BAP-65 class and corresponding observed outcome.

BAP-65 class	Prevalence, N (%)	Composite outcome, N (%)	Mortality	**IMV**
Class 1	126 (4.9)	2 (1.6)	1 (0.8)	1 (0.8)
Class 2	431 (16.6)	14 (3.3)	9 (2.1)	5 (1.2)
Class 3	1592 (61.3)	60 (3.9)	41 (2.6)	24 (1.6)
Class 4	403 (15.5)	44 (11.1)	33 (8.2)	15 (3.8)
Class 5	44 (1.7)	7 (16.3)	7 (15.9)	2 (4.7)

IMV: invasive mechanical ventilation.

supports the generalizability of the results.

Our study had also some limitations. The retrospective nature of the study can translate into a better representation of the usual clinical practice [16], but can also affect data quality and completeness. The diagnosis of COPD should be clinical and instrumental, but in the emergency setting the lack of time and clinical documentation may lead to a misdiagnosis of COPD and its exacerbations, only based on suggestive but not specific symptoms (wheezing and/or respiratory acidosis) and incomplete medical history. We tried to minimize this

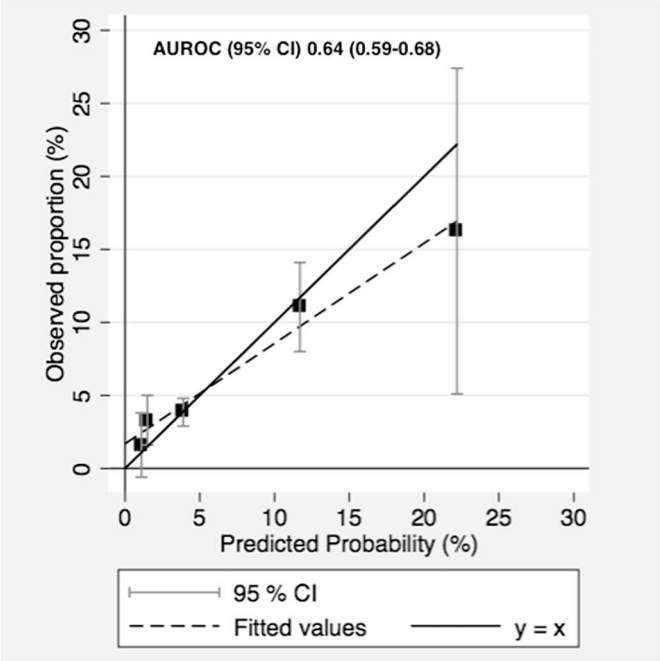

Fig. 1. Calibration plot and AUROC for mortality or invasive mechanical ventilation.
AUROC: area under the receiver operating characteristic curve.

Table 4
Univariate and multivariable analysis for the composite outcome.

Predictor	Missing data not imputed		Missing data imputed	
	OR (95% CI)	p value	OR (95% CI)	p value
	Univariate analysis			
BAP65 class	2.11 (1.64–2.72)	< 0.001	1.71 (1.35–2.16)	< 0.001
Age	1.04 (1.03–1.06)	< 0.001	1.01 (0.99–1.04)	0.184
Sex (female)	0.98 (0.72–1.32)	0.879	0.96 (0.76–1.23)	0.768
Respiratory failure	3.75 (1.99–7.06)	< 0.001	1.82 (0.92–3.61)	0.087
Systolic blood pressure < 90 mmHg	4.68 (1.74–12.61)	0.002	3.61 (1.42–9.24)	0.007
Pneumonia	1.73 (1.21–2.46)	0.003	1.40 (0.89–2.20)	0.144
CCI	1.10 (1-02–1.19)	0.015	1.00 (0.92–1.09)	0.927
Heart failure	1.53 (1.05–2.22)	0.025	1.08 (0.77–1.51)	0.654
Coronary artery disease	0.95 (0.60–1.50)	0.815	0.90 (0.63–1.27)	0.536
Peripheral vascular disease	0.86 (0.50–1.49)	0.595	0.82 (0.51–1.31)	0.400
Cerebrovascular disease	1.06 (0.61–1.83)	0.848	0.83 (0.53–1.28)	0.395
Diabetes without end organ damage	1.04 (0.73–1.47)	0.842	0.91 (0.65–1.28)	0.594
Diabetes with end organ damage	0.78 (0.50–1.21)	0.272	0.63 (0.40–1.01)	0.054
Moderate or severe renal disease	1.20 (0.99–1.45)	0.066	0.99 (0.83–1.19)	0.933
Connective tissue disease	1.00 (0.44–2.25)	0.999	0.66 (0.28–1.56)	0.344
Dementia	2.47 (1.61–3.81)	< 0.001	1.75 (1.18–2.61)	0.005
Peptic ulcer disease	1.62 (0.90–2.91)	0.110	1.14 (0.60–2.15)	0.694
Mild liver disease	1.78 (0.99–3.20)	0.054	1.36 (0.78–2.36)	0.281
Cancer	1.27 (1.04–1.54)	0.018	1.13 (0.98–1.30)	0.084
Metastatic cancer	1.07 (0.93–1.23)	0.337	1.07 (0.94–1.21)	0.293
	Multivariable analysis			
BAP65 class	1.70 (1.29–2.25)	< 0.001	1.74 (1.34–2.25)	< 0.001
Age	1.03 (1.01–1.05)	0.002	Not included*	–
Respiratory failure	3.17 (1.82–5.51)	0.000	Not included*	–
Systolic blood pressure < 90 mmHg	2.32 (0.57–9.50)	0.242	3.12 (1.21–8.00)	0.018

OR: odds ratio, CI: confidential interval, CCI: Charlson comorbidity index.
* Variables not included in multivariable analysis, having not showed a statistically significant association at univariate analysis.

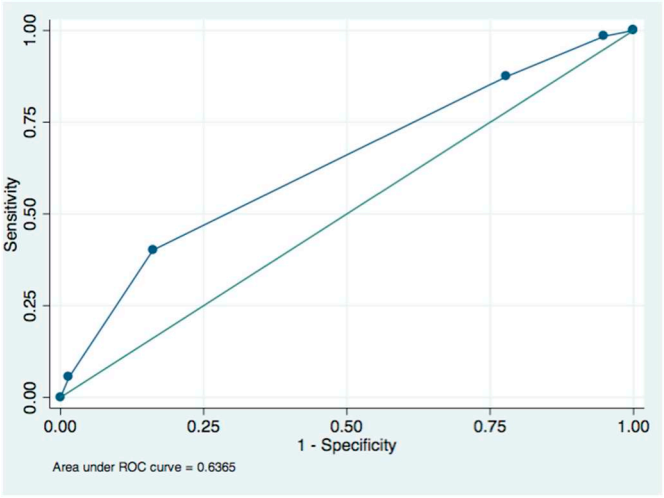

Fig. 2. Receiver-operating characteristic (ROC) curve of the BAP-65 score for the prediction of the composite outcome in-hospital mortality and invasive mechanical ventilation.

issue with a careful patient selection process, as previously described [3]. To address the problem of data completeness, we used data imputation. However, for centers with a high proportion of missing data, we felt it was safer to exclude them from the analysis. This implied excluding 1488 patients form 14 centers. Urea was the missing BAP-65 variable for most of the patients with missing data, as it is not necessarily included in the routine lab screening done in Italian EDs. The characteristics of excluded and included patients did not match exactly. In particular, in centers excluded from the analysis, bronchodilators and steroids were used more frequently, while antibiotics were used less. This can affect the generalizability of our findings. However, we could still base our analysis on a considerable sample of 2908 patients from 20 different centres across the country. Retrieving data on the blood gas analysis of the included patients would have allowed us to better define the respiratory failure, and the need for NIV and IMV. We tried to extract these data in a pilot phase with the first 3 centers but, unfortunately, we realized that the BGA results were seldom reported, so we decided to drop the variable. A longer follow-up would have been appropriate, especially in patients not admitted to the hospital (34%), but it would have required either a prospective design or at least the link with other databases, and those options were not viable for the present study. Compared to the derivation study, the validation cohort was older, had a higher proportion of males, BUN levels were higher, a lower proportion of patients had pulse > 109 bpm, and mortality was higher [4]. These differences can be partially due to the diverse geographical and clinical settings in which the studies have been performed. Concerning the gender distribution, in the derivation study the male/female ratio was 0.82, while we found a ratio of 1.58. However, our findings are more in line with the gender distribution of the disease (being COPD more frequent among men) [17], and perfectly match the findings of a previous Italian study, with a male/female ration of 1.57 [18]. The older age of patients, the higher proportion of males, and the high prevalence of comorbidities (mainly heart failure), can contribute to explain the higher level of blood urea in our patients as compared to the derivation cohort. As a consequence of the different variable distributions, patients in the validation cohort were less likely to be classified in BAP-65 class 1 or 2, and this affected the model's discrimination. These factors can contribute to explaining the lower accuracy of BAP-65 RAM for the prediction of the adverse composite outcome found in our study, compared to the derivation and validation cohorts. On the other end, it is also known that the estimate of the predictive ability of a model form the derivation and internal validation set is usually overoptimistic [7]. This low accuracy and the fact that 95% of patients are categorized in class 2 or higher, therefore having a risk of short term adverse composite outcome ≥3.3%, do not support the use of this RAM for the management of patients in the ED. Several other RAMs have been proposed to be used for patients with COPDE. Among others, the DECAF [19] and the Ottawa prediction rule [20] seem more valuable. However, these rules may be problematic to use in the ED. The DECAF score requires that dyspnoea is assessed using the extended Medical Research Council Dyspnoea (eMRCD) Score [21]. The eMRCD Score is not of commonly used by non-respirologists and might be difficult to implement while dealing with older patients, often presenting dementia or altered mental status. The Ottawa prediction rule entails the execution of the 3 min walking test, and this can hinder its use in everyday practice in a busy and often chaotic environment such as the ED. Moreover, some of the variables contained in these RAMs would not be retrievable retrospectively, making them not suitable for our study. For these reasons, we decided to test the performance of the BAP-65 score, which is based on variables commonly available in the ED setting and easy to calculate. Unfortunately, a simple solution seems not to be the best for a complex disease, affecting complicated patients.

5. Conclusions

In patients attending Italian EDs with a COPDE, the accuracy of the BAP-65 score in the prediction of adverse clinical outcomes does not support its use for the management of patients attending the ED for a COPDE.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.10.018.

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