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Original Article

A one-year risk score to predict all-cause mortality in hypertensive inpatients

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ABSTRACT

The aim of this study was to construct and internally validate a scoring system to estimate the probability of death in hypertensive inpatients. Existing predictive models do not meet all the indications for clinical application because they were constructed in patients enrolled in clinical trials and did not use the recommended statistical methodology. This cohort study comprised 302 hypertensive patients hospitalized between 2015 and 2017 in Spain. The main variable was time-to-death (all-cause mortality). Secondary variables (potential predictors of the model) were: age, gender, smoking, blood pressure, Charlson Comorbidity Index (CCI), physical activity, diet and quality of life. A Cox model was constructed and adapted to a points system to predict mortality one year from admission. The model was internally validated by bootstrapping, assessing both discrimination and calibration. The system was integrated into a mobile application for Android. During the study, 63 patients died (20.9%). The points system prognostic variables were: gender, CCI, personal care and daily activities. Internal validation showed good discrimination (mean C statistic of 0.76) and calibration (observed probabilities adjusted to predicted probabilities). In conclusion, a points system was developed to determine the one-year mortality risk for hypertensive inpatients. This system is very simple to use and has been internally validated. Clinically, we could monitor more closely those patients with a higher risk of mortality to improve their prognosis and quality of life. However, the system must be externally validated to be applied in other geographic areas.

1. Introduction

Cardiovascular disease is the leading cause of death worldwide and represents one of the main causes of hospital admission through emergency services, especially in the elderly [1,2]. The main risk factors for cardiovascular disease are hypertension, diabetes mellitus, dyslipidemia and smoking [3–6]. A greater proportion of patients with these risk factors visit and are admitted to hospital emergency services, with hypertension being the most prevalent factor in their hospital admissions. [2,7]. Similarly, hypertensive patients admitted through hospital emergency services usually have a high comorbidity with other cardiovascular risk factors and a higher likelihood of death during their hospital stay [8]. Thus, it is important to take preventive measures to reduce hospital admissions and mortality.

One of the tools available in clinical practice to evaluate the occurrence of a given event is prediction models. These models can serve as a screening test for a disease or to determine the risk of its development over time (incidence). The prediction is made knowing the status of the risk factors of the disease, and through them we obtain an estimate of the probability of occurrence [9].

In the scientific literature, several papers detail the construction of predictive models of mortality applicable to hypertensive patients (Table 1) [10,11]. Of note, however, these predict cardiovascular or all-cause mortality at 5–10 years, and have been constructed based on populations involved in clinical trials, which are usually very restricted according to the protocols of the trial itself (exclusion criteria). In

Abbreviations: DBP, Diastolic blood pressure; CCI, Charlson Comorbidity Index; CI, Confidence interval; EQ5-D, EuroQol five dimensions questionnaire; EPV, Events-per-variable; PREDIMED, Prevention with Mediterranean diet; RAPA, Rapid Assessment of Physical Activity; SBP, Systolic blood pressure

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Table 1
Published predictive models for mortality in hypertensive patients.

Reference	Patients	Outcome	Time (years)	Variables	Applicability of the model	EPV ≥ 10	Continuous predictors	Missing data	Selection of predictors	Validation
Pocock et al., 2001 [10]	With hypertension included in clinical trials	Cardiovascular mortality	5	Gender, age, smoking, SBP, TC, height, creatinine, myocardial infarction, stroke, LVH, diabetes and antihypertensive drugs	Scoring system and mathematical formula	Yes	Polynomials	Not indicated	Based on the bivariate analysis	Not performed
Huynh et al., 2015 [11]	With hypertension included in clinical trials	Cardiovascular mortality	10	Gender, age, socioeconomic status, alcohol consumption, smoking, diabetes, waist-hip ratio and physical activity	Not indicated	Yes	Linear analysis and categorizations	Not indicated	Stepwise method based on AIC, BIC, C-statistics using bootstrapping	C-statistic, calibration plot and bootstrapping
Huynh et al., 2015 [11]	With hypertension included in clinical trials	All-cause mortality	10	Gender, age, socioeconomic status, alcohol consumption, smoking, body mass index, cholesterol medication and glucose	Not indicated	Yes	Linear analysis and categorizations	Not indicated	Stepwise method based on AIC, BIC, C-statistics using bootstrapping	C-statistic, calibration plot and bootstrapping

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EPV, events-per-variable; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; TC, total cholesterol.

addition, the calculation of risk presents difficulties in two of these models, since the authors do not indicate how to calculate the probability of death. Finally, their statistical methodology has limitations regarding the guidelines to construct and internally validate a predictive model [12,13]. These guidelines indicate that a predictive model should be easy for the clinician to use, have an events-per-variable (EPV) greater than or equal to 10 (sample size to construct a predictive model), analyze the functional form for the continuous predictors (not use them linearly or by categorizations), impute the missing data (not analyze only complete cases), select the variables of the model considering the overall goodness of fit (not by each variable separately) and perform validation correctly (discrimination and calibration by bootstrapping) [12,13]. None of the models of mortality in a hypertensive population listed in Table 1 meets all these requirements.

Taking into account that hypertensive inpatients have a high risk of mortality [8] and that in the scientific literature we found no models to predict this risk that complied with all the guidelines for their clinical applicability [12,13], we conducted a cohort study with a one-year follow-up to assess this relevant issue. With the data from this cohort, we estimated a scoring system that was then integrated into a mobile application for Android. Using this application, in a matter of seconds, the clinician can estimate the probability of death in this type of patient, thus providing health professionals a tool with which to improve decision-making in a hypertensive inpatient population.

2. Materials and methods

2.1. Study population

The study population corresponded to all hypertensive patients residing in the healthcare area of the Elda Valley who were admitted through the emergency department of the General University Hospital of Elda. This healthcare area covers a total of 198,090 inhabitants and is located in the province of Alicante (southeast of Spain). The healthcare system is free and universal for the entire population. The General University Hospital of Elda (the only hospital in the healthcare area) is a public institution with 513 beds. At present, its emergency department attends approximately 57,000 patients per year, which is equivalent to about 160 general emergencies per day in adults, excluding the specialty of obstetrics and gynecology [14,15].

2.2. Study design and participants

This study comprised a cohort of hypertensive patients admitted through the emergency department of the General University Hospital of Elda during 2015. A patient was considered hypertensive when diagnosed as such by the primary care physician through the ICD-9-CM code (401.x). The sample was selected by means of a simple random sampling of days during the year 2015. Included in the study were all hypertensive patients who wished to participate and had been admitted by the hospital emergency department on the selected days. Each patient was followed from admission (baseline) until the end of the study (February 17, 2017).

2.3. Variables and measurements

The main study variable was time-to-death, considering mortality from any cause. To assess mortality, the following sources of information were analyzed at the end of the study: (1) clinical history of the patient: to determine if the patient had returned to the health center for any reason or was marked as deceased. In the event the patient had come to the health center for any reason, we would have the certainty that he had not died (censored data). In addition, if the patient appeared as deceased and there were questions regarding the data found, we telephoned the relatives to corroborate the date of death and its cause; and (2) Hospital discharge: all deaths of hospitalized patients are

recorded (date and cause) in this database.

As secondary variables (potential factors in the predictive model), the following were measured at baseline: age (years), gender, smoking pack-years (twenty cigarettes smoked daily), systolic and diastolic blood pressure (SBP and DBP, in mmHg), Charlson Comorbidity Index (CCI) [16], Rapid Assessment of Physical Activity (RAPA) [17], Prevention with Mediterranean diet (PREDIMED) diet assessment tool [18] and EuroQol five dimensions questionnaire (EQ5-D) (mobility, self-care, usual activities, pain/discomfort and anxiety/depression, in addition to health status) [19]. An interview with the patient was conducted during the admission process to obtain the following series of variables: age, gender, smoking, physical activity, diet and quality of life. The clinical history was also analyzed to obtain the CCI. Finally, blood pressure was measured following the current consensus during evaluation in the emergency department. These variables were selected because most of them are cardiovascular risk factors that can increase the risk of death. The CCI is a mortality score and, consequently, a higher score is associated with a higher probability of death. Finally, a healthy lifestyle with a high quality of life could be associated with improved survival.

2.4. Sample size

During the study period there were 302 patients, 63 of whom died. Given that the objective of this work was to construct a prediction model, the sample size should be based on the EPV, which must be greater than or equal to 10. With 63 events, we had a sample size to estimate a predictive model with a maximum of 6 prognostic variables [20].

2.5. Statistical methods

Qualitative variables were described using absolute and relative frequencies, while quantitative variables were measured by means and standard deviations. As recommended [12], prior to the construction of the model, multiple imputation of missing data was performed to minimize selection bias by using only complete cases. Instead of performing categorizations or linearly studying the continuous predictors, their functional form was analyzed through the score test. This was done by comparing the powers of the predictor, retaining the degree that showed no statistically significant differences with the highest degree. For example, when we compared the linear predictor with the linear + quadratic predictor and there were no differences between them, we would take the linear one, because it is simpler. In addition, the ordinal qualitative variables were considered to be quantitative, using 0 as the lowest category, 1 the next and so on. The unadjusted hazard ratios were then estimated for each secondary variable, including the comorbidities of the CCI. These were not taken into account for the multivariate model (collinearity issues).

After analyzing the continuous predictors and taking into account that we could enter a maximum of 6 variables, we checked all the possible combinations of 1, 2, 3, 4, 5 and 6 predictors in a multivariate Cox regression model (a total of 43,795 combinations, counting powers of degree greater than or equal to two that showed significance in the score test), estimating the C statistic in all of them. The combination with the highest C-statistic value was selected to make mortality predictions, and on the model with these variables the hypothesis of proportional risks was corroborated through graphical and analytical tests. The methodology of the Framingham study was applied to this multivariate model to adapt the hazard ratios to a points system and thereby make it easier to use in order to be implemented in daily clinical practice [21]. This method, through a weighting of the coefficients of the model and categorizations of the risk factors, associates a score to each risk factor, which is added to that of all of them. The total score has an associated probability of mortality [21], which was set at a period of one year. Note that it is a shorter period than in the existing models (Table 1). However, we emphasize that our patients are hospitalized and therefore have a higher risk of mortality; thus, studying a shorter period of time is relevant.

To internally validate the prediction model, both discrimination and calibration should be corroborated [12]. Discrimination was assessed by the C statistic and calibration by a graph comparing the observed probabilities of the event with those expected by the model. To obtain the observed risk, linear splines were used, as recommended in the literature [22]. The entire validation process was performed by bootstrapping, as this is the recommended procedure to validate a predictive model [12].

All analyses were performed with a significance of 5% and for each relevant parameter its associated confidence interval (CI) was calculated. The statistical packages used were IBM SPSS Statistics 24 and R 2.13.2.

2.6. Ethical issues

This study was approved by the Ethics Committee of the Elda Health Department. Informed consent was requested from all patients, and they were informed of all the study characteristics. The study was conducted in accordance with the basic principles of the Declaration of Helsinki World Medical Association and met the standards described in the European Union guidelines on good clinical practice.

2.7. Mobile App

The points system was implemented in a mobile application for the Android operating system. With this app, the probability of mortality one year after admission through a hospital emergency department can be calculated, without the need for mathematical operations. This App is available free of charge on Google Play and its name is *Hypertension mortality*.

3. Results

During the development of the study, 63 of the 302 patients died (20.9%, 95% CI: 16.3–25.4%) during a mean follow-up time of 1.48 ± 0.60 years, equivalent to an incidence density of 14 deaths per 100 person-years (95% CI: 11–18). The descriptive characteristics of the sample analyzed are shown in Table 2. Here we highlight a mean age of 62.9 years, high tobacco consumption (mean of 21.2 pack-years), high comorbidity index (mean CCI of 3.2), high adherence to the Mediterranean diet (mean of 10 points) and low quality of life, since there was a high prevalence of problems. The mean overall quality of life score was 53.5 points. The causes of admission were the following diseases or conditions: 74 (24.5%) infectious, 1 (0.3%) tumors, 5 (1.7%) hematologic, 13 (4.3%) endocrine and metabolic, 6 (2.0%) nervous system and organs of the senses, 117 (38.7%) circulatory, 30 (9.9%) respiratory, 48 (15.9%) digestive, 4 (1.3%) osteomuscular and 4 (1.3%) genitourinary.

Multiple imputation was performed for the following number of missing data in the study variables: two for age, eight for pack-years, four for blood pressure (SBP and BPD), one for CCI and one for mobility in the EQ-5D. After this imputation, the functional form for the continuous predictors was analyzed, presenting the following *p*-values when comparing the continuous predictor with the linear + quadratic predictor: age ($p < .001$), pack-years ($p = .128$), SBP ($p = .610$), DBP ($p = .743$), CCI ($p = .636$), RAPA aerobic ($p = .025$), RAPA strength & flexibility (without quadratic convergence), PREDIMED ($p = .831$), mobility ($p < .001$), personal care ($p = .009$), daily activity ($p = .272$), pain ($p = .379$) and EQ-5D score ($p = .799$). We then compared linear + quadratic with linear + quadratic + cubic, obtaining: age ($p = .005$), RAPA aerobic ($p = .610$), mobility and personal care (without cubic convergence). Finally, when comparing the addition of the fourth power to the age, there was no convergence, so

Table 2
Descriptive characteristics, unadjusted and adjusted hazard ratios for predicting mortality in hypertensive inpatients.

Variable	Total n = 302 n(%)/x ± s	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Mortality	63(20.9)	N/A	N/A	N/A	N/A
Age (years)	62.9 ± 10.9	1.00(1.00–1.00)	0.638	N/M	N/M
Age^2 (years^2)	N/A	N/A	N/A	N/M	N/M
Male gender	154(51.0)	1.05(0.64–1.73)	0.838	1.27(0.76–2.12)	0.357
Smoking pack-years	21.2 ± 32.8	1.00(0.99–1.01)	0.910	N/M	N/M
SBP (mmHg)	141.8 ± 26.4	0.99(0.98–1.00)	0.137	N/M	N/M
DBP (mmHg)	77.4 ± 16.9	0.99(0.97–1.00)	0.099	N/M	N/M
CCI	3.2 ± 2.4	1.19(1.10–1.30)	< 0.001	1.17(1.07–1.28)	< 0.001
RAPA (aerobic)	2.4 ± 1.4	0.83(0.67–1.02)	0.071	N/M	N/M
RAPA (aerobic)^2	N/A	N/A	N/A	N/M	N/M
RAPA (strength & flexibility)	0.0 ± 0.2	N/A	N/A	N/M	N/M
PREDIMED	10.0 ± 1.8	0.90(0.79–1.03)	0.139	1.00 (0.86–1.16)	0.967
Mobility (EQ5-D):					
No problems	115(38.1)	2.50(1.75–3.58)	< 0.001	N/M	N/M
Some problems	131(43.4)				
Confined to bed	55(18.2)				
Mobility (EQ5-D)^2	N/A	N/A	N/A	N/M	N/M
Self-care (EQ5-D):					
No problems	141(46.7)	2.39(1.72–3.31)	< 0.001	0.38(0.11–1.29)	0.120
Some problems	105(34.8)				
Unable	56(18.5)				
Self-care (EQ5-D)^2	N/A	N/A	N/A	2.10(1.18–3.76)	0.012
Usual activities (EQ5-D):					
No problems	179(59.3)	2.44(1.79–3.31)	< 0.001	1.43(0.85–2.43)	0.183
Some problems	80(26.5)				
Unable	43(14.2)				
Pain/Discomfort (EQ5-D):					
None	138(45.7)	1.08(0.81–1.43)	0.610	N/M	N/M
Moderate	68(22.5)				
Extreme	96(31.8)				
Anxiety/Depression (EQ5-D):					
None	261(86.4)	0.62(0.35–1.09)	0.098	N/M	N/M
Moderate	10(3.3)				
Extreme	30(9.9)				
Health state (EQ5-D)	53.5 ± 20.1	0.98(0.97–0.99)	0.004	N/M	N/M
Myocardial infarction	87(28.8)	1.60(0.96–2.66)	0.070	N/A	N/A
Congestive heart failure	114(37.7)	1.14(0.69–1.88)	0.609	N/A	N/A
Peripheral vascular disease	71(23.5)	2.06(1.23–3.44)	0.006	N/A	N/A
Cerebrovascular disease	79(26.2)	1.06(0.71–1.59)	0.780	N/A	N/A
Dementia	22(7.3)	1.71(0.78–3.75)	0.182	N/A	N/A
Chronic pulmonary disease	83(27.5)	1.20(0.71–2.05)	0.491	N/A	N/A
Connective tissue disease	3(1.0)	N/A	N/A	N/A	N/A
Ulcer	31(10.3)	1.17(0.53–2.56)	0.701	N/A	N/A
Mild liver disease	10(3.3)	1.01(0.25–4.11)	0.994	N/A	N/A
Diabetes	78(25.8)	0.98(0.55–1.73)	0.939	N/A	N/A
Hemiplegia	10(3.3)	0.42(0.06–3.05)	0.394	N/A	N/A
Moderate/Severe renal disease	40(13.2)	2.22(1.23–4.02)	0.008	N/A	N/A
Diabetes with end organ damage	39(12.9)	1.46(0.76–2.81)	0.251	N/A	N/A
Any tumor	68(22.5)	1.56(0.91–2.68)	0.103	N/A	N/A
Leukemia	2(0.7)	N/A	N/A	N/A	N/A
Lymphoma	0(0)	N/A	N/A	N/A	N/A
Moderate/Severe liver disease	12(4.0)	2.57(1.03–6.42)	0.043	N/A	N/A
Metastatic solid tumor	5(1.7)	3.96(1.24–12.7)	0.020	N/A	N/A
Acquired immune deficiency syndrome	0(0)	N/A	N/A	N/A	N/A

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; DBP, diastolic blood pressure; EQ5-D, EuroQol five dimensions questionnaire; HR, hazard ratio; n(%), absolute frequency (relative frequency); N/A, not applicable; N/M, not in the multivariate model; PREDIMED, PREvención con DIeta MEDiterránea (adherence to Mediterranean diet); RAPA, Rapid Assessment of Physical Activity; SBP, systolic blood pressure; x ± s, mean ± standard deviation.
The EQ5-D variables were analyzed as quantitative variables, defined in the following form: *lowest category*→0, *medium category*→1 and *highest category*→2).
The variables with a squared power had statistical significance compared to those with a linear association (p-value for the score test < 0.05).
Goodness-of-fit of the model: χ^2 = 65.7, p < .001, C-statistic = 0.77 (standard error 0.037). Number of tested combinations: 43,795.

we were left with the cubic power. However, after estimating the multivariate models, the cubic term had to be excluded for reasons of convergence, analyzing only the linear and quadratic term. Consequently, the variables on which the quadratic term was analyzed were: age, RAPA aerobic, mobility and personal care. The individual risks for each secondary variable (including the CCI comorbidities) are shown in Table 2. Of note were statistically significant results for a worse quality of life and some comorbidities (peripheral vascular disease, moderate/severe renal disease, moderate/severe liver disease and metastatic solid tumor). These risks are shown at a descriptive level because for the multivariate model the results had to be adjusted for confounders.

After the previous treatment of the data, 43,795 Cox regression models were estimated. The model selected contained the variables: gender, CCI, PREDIMED, personal care (linear and quadratic) and daily activities. Table 2 shows the hazard ratios associated with these predictors, which obtained a C statistic of 0.77 (standard error 0.037) for the Cox model without violating the hypothesis of proportional risks

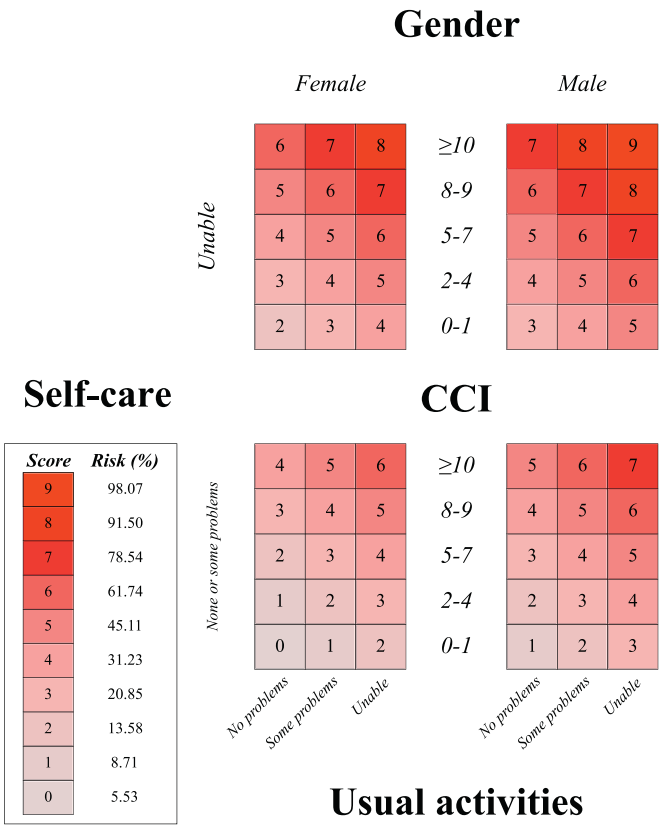

Fig. 1. Scoring system to predict one-year risk of all-cause mortality in hypertensive inpatients.
CCI, Charlson Comorbidity Index. *Self-care* and *usual activities* are questions of the EuroQol five dimensions questionnaire (EQ-5D).

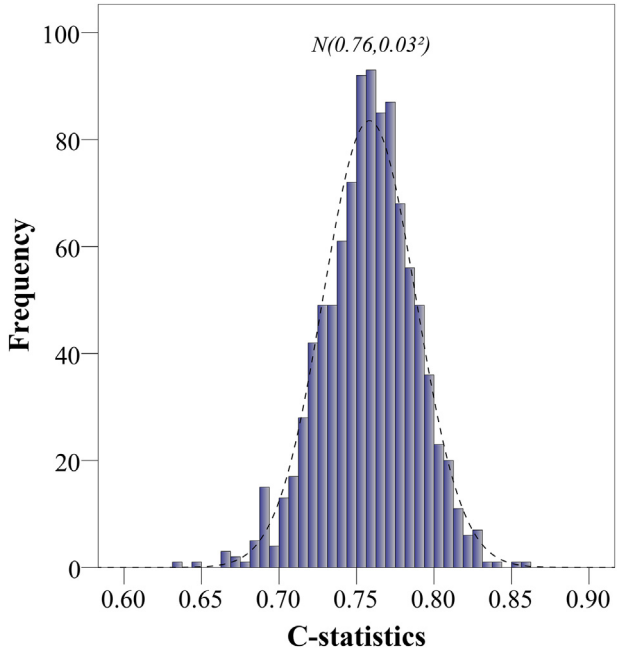

Fig. 2. C-statistic distribution for the validation of our scoring system using bootstrap methodology.

(p = .098), with baseline survival at one year of 0.863323 on the mean of the predictors. The adaptation of the multivariate model to a points system is shown in Fig. 1, where the risk of death may be calculated immediately. Regarding the internal validation by bootstrapping, the distribution of the C statistic (Fig. 2) had a mean value of 0.76 and the smooth curve for the probability distribution was adjusted satisfactorily to the perfect condition (observed = expected) (Fig. 3).

4. Discussion

4.1. Summary

This study developed a very simple to use prediction model (points system and mobile application) to determine the probability of death at one year in a hypertensive patient admitted through the emergency department. In addition, the model was developed following the international standards for prediction models [12] and presented very good results in its validation.

4.2. Strengths and limitations of the study

The main strength of our study is the development and internal validation of a prediction model to estimate the probability of death in hypertensive inpatients. To our knowledge no such predictive model has been available until now. In addition, we addressed this clinical question through a prospective cohort study with primary data and using the statistical methodology recommended by the leading international experts in the development of predictive models in health sciences. [12]. Another strength lies in having used a randomized sample when most studies use a convenience sample. Furthermore, the applicability of the model for the clinician is very simple, as both the points system and the mobile application can be used. As limitations, we note that it would have been interesting to have had a larger set of patients, which would have allowed introducing more variables in the model or introducing splines for the quantitative variables, and thereby improving the discrimination of the model. Additionally, we could have externally validated our model in another data set using the records of other hospitals in our area (pending for future studies). Finally, we could have collected more secondary variables in order to improve the prognostic value of our model, although it was nevertheless very satisfactory (discrimination and calibration).

4.3. Comparison with the existing literature

When comparing the clinical issues of our model with existing models (Table 1), several points should be addressed. First, we observed that the patients from the other studies come from clinical trials. This produces an important selection bias, since a trial generally has very specific inclusion and exclusion criteria, and a high percentage of the participants receive a specific type of treatment and hence they do not correspond to a true clinical practice population. [12]. Our sample, instead, was randomly selected from a clinical practice population, which ensures the applicability of the results. Second, in two of the three models the probability of death cannot be obtained, and in the rest this probability must be calculated using a mathematical formula. In our case, by simply looking at the box corresponding to the characteristics of our patient (Fig. 1), the score is obtained and the risk is given automatically in the legend. This process is even faster when using the mobile application. On the other hand, the prediction period of the other models is much longer (Table 1). This, however, is a consequence of the fact that our patients already have a high baseline risk of mortality, since they have been admitted to the hospital. Proof of this is the high proportion of deaths during the follow-up period. Finally, the source of the data used in the other models is > 20 years old, while ours is much more recent.

If we now analyze the statistical issues, we see that the other studies use techniques that do not adhere to the international recommendations [12]. First, two of the models did not study the functional form for continuous predictors, but rather they performed categorizations and linear analyses without justification. Furthermore, none of the studies

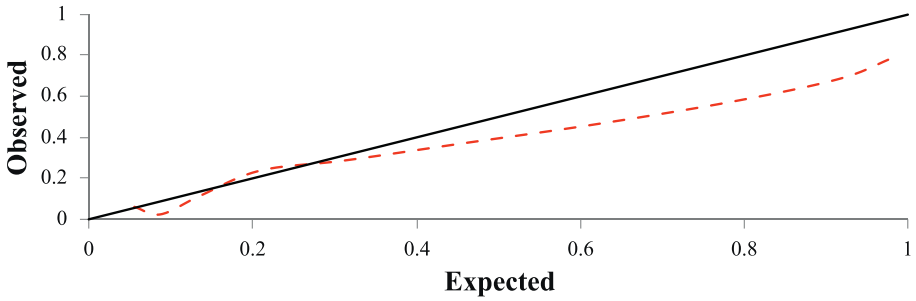

Fig. 3. Smooth calibration plots for the validation of our scoring system using bootstrap methodology.
The black line is the perfect condition and the red line shows the result of our calibration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

comments on what occurred with patients that had missing data. Another study used bivariate analysis to determine the variables of the final model, when this is not at all recommended [12]. Finally, no study correctly performed the internal validation: one did not analyze it and the other two did not apply smooth curves [22]. In contrast, we applied all the points of the recommendations, with the aim of achieving a mathematically correct model that can be applied in the clinical setting to reduce the incidence of mortality in this type of patient.

4.4. Implications to research and clinical practice

We opened two possible lines for future research. The first is to design studies to externally validate the predictive model constructed. If discrimination and calibration results are good, it can then be applied in other geographic areas. Second, we propose the development of new predictive models following our methodology in hypertensive patients in the primary care setting, increasing the follow-up time and considering variables that are easy to obtain. Another option would be to recalibrate the model constructed in this paper.

Clinicians now have a new tool to obtain the probability of mortality of the hypertensive patient after hospital admission. For its application, we would need to know the most serious diseases of the patient (CCI), the gender of the patient and the problems encountered in daily life (personal care and daily activities). In other words, using information that is easy to obtain, the mortality risk can be calculated in a few seconds. This would provide a great clinical benefit, enabling the clinician to determine which patients have a high risk of mortality and, consequently, require closer and more comprehensive management. In addition, it would be interesting to assess through a clinical trial whether having a caregiver decreases this risk, as problems associated with poor quality of life would be reduced.

5. Conclusions

We constructed and internally validated a points system to predict mortality in hypertensive inpatients at one year. The system incorporates variables that are easy to obtain in clinical practice and can be used to stratify the risk of patient mortality, to subsequently perform a closer follow-up or design individualized interventions in those with a high risk of death. Our work is an important step toward developing and promoting more simple and practical predictive models for very common diseases with a high morbidity. More studies will need to be conducted on larger and more heterogeneous samples of patients to enable the universal applicability of our scoring system.

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Conflict of interests

Nothing to declare.

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