Multisystem chronic illness prognostication in non-oncologic integrated care

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ABSTRACT

Objectives To develop a mortality-predictive model for correct identification of patients with non-cancer multiple chronic conditions who would benefit from palliative care, recognise predictive indicators of death and provide with tools for individual risk score calculation.

Design Retrospective observational study with multivariate logistic regression models.

Participants All patients with high-risk multiple chronic conditions incorporated into an integrated care strategy that fulfil two conditions: (1) they belong to the top 5% of the programme's risk pyramid according to the adjusted morbidity groups stratification tool and (2) they suffer simultaneously at least three selected chronic non-cancer pathologies (n=591).

Main outcome measure 1 year mortality since patient inclusion in the programme.

Results Among study participants, 201 (34%) died within the 1 year follow-up. Variables found to be independently associated to 1 year mortality were the Barthel Scale (p<0.001), creatinine value (p=0.032), existence of pressure ulcers (p=0.029) and patient global status (p<0.001). The area under the curve (AUC) for our model was 0.751, which was validated using bootstrapping (AUC=0.751) and k-fold cross-validation (10 folds; AUC=0.744). The Hosmer-Lemeshow test (p=0.761) showed good calibration.

Conclusions This study develops and validates a mortality prediction model that will guide transitions of care to non-cancer palliative care services. The model determines prognostic indicators of death and provides tools for the estimation of individual death risk scores for each patient. We present a nomogram, a graphical risk calculation instrument, that favours a practical and easy use of the model within clinical practices.

INTRODUCTION

Background

Patients with multiple chronic conditions have become a growing concern for clinicians and health system administrators.[1] At present, approximately 50% of all individuals in the general population suffer at least one chronic disorder, and around a quarter suffer several chronic disorders at the same time.[2]

This typology of patients is more common in elderly strata of the population,[3] among which functional loss and frailty are high. The number of people reaching old age is growing, and consequently the prevalence of patients with multiple chronic diseases is increasing.[4]

As a result of the increase of prevalence of multimorbidity, concerns over health systems' sustainability are arising. Patients with multiple chronic conditions use healthcare resources in an intensive and frequent way, and despite representing a small number of patients they account for the majority of the budget in some organisations.[5 6]

Efforts to contain cost and provide appropriate care focus on integrated care models that aim to treat multiple pathologies in a uniform and coordinated manner, improving patient quality of life and encouraging less use of resources. However, not all patients included in integrated care models benefit from them. Very severe patients, who belong to the apex of the Kaiser pyramid, have very high mortality rates and do not achieve improvements neither in their quality of life nor in their clinical progression despite high resource utilisation.[7 8]

These patients with advanced disease could benefit from programmes focused on end-of-life care instead, focusing on

improving their quality of life and putting aside ineffective and expensive treatments.[9 10]

Despite the fact that the number of deaths attributable to chronic non-cancer diseases exceed those of cancer[11] and the potential benefits that palliative care could provide, this type of care has traditionally been reserved for patients with cancer. There is evidence for this unmet need, with very low rates of non-oncological patients included in palliative care programmes. In Spain, France or Germany patients with chronic disease in palliative care account for <10% of utilisation of these services, and at a European level, this figure drops to 6%.[12]

Among the obstacles that are causing the delay in the implementation of these specific palliative care models, one in particular stands out. Determining exactly the moment in which the deterioration of a patient gives way to the terminal phase of life is complicated, especially in patients with more than one advanced-stage disease with 'entry–re-entry' trajectories.[9 13]

The identification of predictive indicators of death can help the development of objective criteria for a correct and timely identification of those patients in whom the terminal phase of their life will happen in the near future. Obstacles presented by health professionals could be overcome, providing tools to avoid further delays in transitions towards palliative care for patients with multiple chronic conditions.

Organisations like Medicaid and Medicare require a prognosis of ≤6 months to be eligible for hospice benefits.[13] However, predictive models that estimate 6 month mortality in patients with non-cancer have shown a lack of ability to discriminate patients accurately. Frequent exacerbations and entry–re-entry trajectories make short-run estimation unpredictable in nature and consequently less accurate.[9 14]

Using longer time frames, such as 1 year mortality, is therefore more appropriate. Additional benefits arise from this approach, since it allows early identification of patients, rather than identifying them in their last stages of life when the terminal decline has begun. This allows reorientation of clinical strategies towards quality of life improvements and reduction of patient distress, instead of continuing with aggressive treatments with no curative effects.[15] Moreover, this reduction in ineffective treatments and avoidable hospitalisations generates cost savings and greater efficiency to the system.

This study develops a 1 year mortality predictive model for its use as a risk assessment tool that can guide the correct identification of patients who are near to their terminal phase of their lives.

Objectives

Three objectives have been set in this study. The first one is to develop a mortality predictive model, the second objective is to identify predictors of death and the third objective is to provide with a nomogram to healthcare professionals to calculate individual risk scores.

METHODS

Data and participants

The context of this study is the integrated care programme for patients with multiple chronic conditions of the Spanish region of Navarre (640.000 inhabitants), implemented in 2016. Data were obtained from the specific integrated care programme database, which is anonymised. This database is population-based, and aggregate demographic data together with other data from several sources, including primary care and hospital electronic clinical histories, hospital nursing history, intra and extra hospital electronic prescriptions, as well as degree of dependency recognition according to Spanish Law.[16]

The study population consists of all high-risk patients with multiple chronic conditions from the region incorporated into the integrated care strategy from April 2016 to August 2018 that completed at least a 1 year follow-up from enrolment, or died before follow-up completion. Those patients for whom 1 year follow-up was not completed because the study period came to an end and had not died were excluded from analysis to avoid censoring problems.

Programme conditions to qualify for enrolment are the following: (1) they belong to the top 5% of the programme's risk pyramid according to the adjusted morbidity groups (GMAs) stratification tool,[17–19] which is similar to other tools such as clinical risk groups and (2) they suffer at least three of the following non-cancer pathologies—heart failure, dementia, ischaemic heart disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, asthma, chronic renal failure or cirrhosis.[20] A total of 885 patients were enrolled into the programme in the study time, from which 591 were included in this study, and 294 were censored.

Variables

The dependent variable for this study is defined as the occurrence of death within the first year that a patient spends in the high-risk programme; in other words, 1 year mortality since enrolment.

A broad range of predictor variables were incorporated into the analysis. These are not disease-specific variables, but general criteria that can be applied to a heterogeneous population of patients with different combinations of chronic illnesses.

These include demographic data (age, sex, patient living in nursing home or not, presence of informal carer), functional status variables (Barthel scale,[21] Lawton and Brody Scale[22] and degree of dependency), nutritional values (serum albumin), renal deterioration indicators (creatinine, albumin/creatinine index), prevalence of selected non-cancer conditions, total number of selected comorbidities, prevalence of pressure

skin ulcers, intake of opioids and psycholectics, total number of active prescriptions and GMA score.

All variables represent real-world data and were collected at patient inclusion into the high-risk programme. At that time, all patients undergo an assessment in which doctors, nurses and social workers classify patients into four levels of severity (low, moderate, high and very high). All three classifications are then combined in a meeting in which all healthcare professionals involved in the assessment produce a 'global status' variable, with the same levels of severity.[8]

Multiple imputation was used to fill in missing values, under a missing at random assumption, with the purpose of avoiding any possible bias that incomplete data would have caused.[23]

Statistical analysis

Descriptive statistics are provided including the mean and SD for continuous variables, and number of people and percentage for categorical variables, both for the whole population, and by 1 year mortality status.

A logistic regression model was fitted following the methodology defined by Hosmer and Lemeshow[24] and Steyerberg.[25] Univariate analysis was performed on each variable as a first step of model selection, showing the level of association between 1 year mortality and every predictor variable. When a variable had a p value significance level of $p \leq 0.25$, it was considered further for multivariate modelling. Subsequently, a model containing all of the preselected variables from the univariate analysis was fit, and insignificant variables were deleted one by one in separate steps until a final model was reached.

Discriminative ability of the model was measured using the receiver operating characteristic (ROC) curve and its associated area under the curve (AUC), which evaluates discrimination of the model across all probability cut-offs that classify the output as positive or negative. Whenever two variables measured the same aspect (eg, Barthel Scale vs degree of dependency), the variable that yielded a higher AUC was selected for the final model.

Regarding goodness of fit, the Hosmer-Lemeshow test and calibration plots were used. To validate the model, we used k-fold cross-validation with 10 random folds and bootstrap validation, rather than the traditional method of splitting the dataset into developing and validation samples, which has proved to be inefficient in comparison to the methods mentioned above.[25] Results are expressed in terms of ORs, and analyses were performed using STATA 15.0.

To favour the applicability of the prediction model and the introduction of individual risk assessment in clinical practices, we provide a nomogram that was created with the 'nomolog' command in STATA.[26] This graphical calculation instrument uses the results of our model and constitutes an easy and rapid way of providing individual estimations of the probability of death for each patient.

RESULTS

Table 1 shows descriptive statistics of all predictor variables considered in analysis, for the whole sample, and by 1 year mortality status. This table also shows univariate logistic regression p values, showing level of significance of the relationship between each variable with 1 year mortality. The profiles of those who die within 1 year after inclusion of the programme and those who live can be extracted from this table.

There is a significant difference in age between those who died and those who survived the follow-up, but sex is not a significant variable, with similar proportions of males and females in both groups. Living in a nursing home, or having an informal carer did not have any effects on death.

Functional status variables were good prognostic indicators of death, with the Barthel Scale and the degree of dependency showing a strong association with mortality. However, when the Lawton and Brody Scale was used, functional deterioration was not a significant variable.

Individuals who died showed lower nutritional values as measured by serum albumin, and higher creatinine values, indicating renal deterioration. In contrast, no significant differences were reported in the albumin/creatinine index. Pressure ulcers were much more frequent in those who died, with significant differences.

Regarding prevalence of non-cancer indications, those patients with dementia showed higher association with mortality. All other indications showed similar prevalence across groups, and no significant differences were observed in number of selected comorbidities.

Both groups had a similar number of active prescriptions at the time of inclusion into the programme, and no differences in the intake of opioids and psycholectics were observed. The GMA score was not a significant variable when predicting death.

Significant differences between groups were observed in the professional-rated variables, such as clinical severity (only at the very severe classification level), nursing needs (at the severe and very severe classification levels) and global status. However, social needs were similar for all patients.

Results from descriptive statistics and univariate logistic analyses can inform about the representative profile of those high-risk patients who die within 1 year follow-up. In general, they are elderly patients (≈85 years old) being cared by a third person, with functional, nutritional and renal decline. They are clinically severe individuals with high nursing care needs, but with the same social needs as those who do not die. The most widespread conditions among this type of patients are heart failure (72.14%), diabetes (71.64%)

Table 1 Descriptive statistics and univariate logistic regression results

Variable	1 Year mortality			Univariate logistic ORs	Univariate logistic p values
	All patients n=591	Alive n=390 (66%)	Dead n=201 (34%)		
Age	83.60±8.10	82.74±8.47	85.25±7.07	1.043	<0.001
Sex					
Female	255 (43.15%)	170 (43.59%)	85 (42.29%)		
Male	336 (56.85%)	220 (56.41%)	116 (57.71%)	1.054	0.762
Living in nursing home	12 (2.03%)	9 (2.31%)	3 (1.49%)	0.641	0.509
Presence of informal carer	532 (90.02%)	346 (88.72%)	186 (92.54%)	1.539	0.295
Barthel Scale	58.13±30.2	65.04±28.42	44.74±29.11	0.978	<0.001
Lawton and Brody Scale	3.16±1.81	3.29±1.86	2.89±1.68	0.913	0.125
Degree of dependency					
Not dependent	112 (18.95%)	96 (24.62%)	16 (7.96%)		
Degree I: moderate	295 (49.92%)	204 (52.31%)	91 (45.27%)	1.780	0.058
Degree II: severe	123 (20.81%)	60 (15.38%)	63 (31.34%)	3.705	<0.001
Degree III: great dependency	61 (10.32%)	30 (7.69%)	31 (15.42%)	4.537	<0.001
Serum albumin (g/dL)	3.79±0.43	3.85±0.41	3.67±0.43	0.422	<0.001
Creatinine (mg/dL)	1.55±0.81	1.51±0.76	1.63±0.89	1.193	0.094
Albumin/creatinine index					
≤30 mg/g: normal	359 (60.74%)	238 (61.02%)	121 (60.20%)		
30–300 mg/g: moderate	167 (28.26%)	112 (28.72%)	55 (27.36%)	0.913	0.653
≥300 mg/g: high	65 (11.00%)	40 (10.26%)	25 (12.44%)	1.256	0.419
Prevalence of diabetes	428 (72.42%)	284 (72.82%)	144 (71.64%)	0.943	0.761
Prevalence of chronic renal failure	410 (69.37%)	274 (70.26%)	136 (67.66%)	0.886	0.517
Prevalence of ischaemic heart disease	293 (49.58%)	195 (50.00%)	98 (48.76%)	0.951	0.775
Prevalence of heart failure	402 (68.02%)	257 (65.90%)	145 (72.14%)	1.340	0.124
Prevalence of cerebrovascular disease	198 (33.50%)	127 (32.56%)	71 (35.32%)	1.131	0.501
Prevalence of COPD	176 (29.78%)	122 (31.28%)	54 (26.87%)	0.807	0.266
Prevalence of asthma	123 (20.81%)	84 (21.54%)	39 (19.40%)	0.877	0.545
Prevalence of dementia	110 (18.61%)	65 (16.67%)	45 (22.39%)	1.442	0.091
Prevalence of cirrhosis	46 (7.78%)	33 (8.46%)	13 (6.47%)	0.748	0.393
Number of selected comorbidities	3.70±0.84	3.69±0.85	3.71±0.82	1.017	0.873
Presence of pressure ulcers	187 (31.64%)	103 (26.41%)	84 (41.79%)	2.000	<0.001
Intake of opioids	77 (13.03%)	54 (13.85%)	23 (11.44%)	0.804	0.412
Intake of psycholectics	54 (9.14%)	31 (7.95%)	23 (11.44%)	1.496	0.165
Number of active prescriptions	8.05±3.51	8.07±3.53	8.03±3.48	0.997	0.904
GMA score	23.50±6.72	23.69±6.68	23.14±6.79	0.987	0.342
Clinical severity					
Mild	2 (0.34%)	2 (0.51%)			
Moderate	69 (11.68%)	54 (13.85%)	15 (7.46%)		
Severe	257 (43.49%)	178 (45.64%)	79 (39.30%)	0.901	0.578
Very severe	263 (44.50%)	156 (40.00%)	107 (53.23%)	7.902	<0.001
Nursing needs					
Mild	47 (7.95%)	40 (10.26%)	7 (3.48%)		
Moderate	204 (34.52%)	160 (41.03%)	44 (21.89%)	1.493	0.383
Severe	213 (36.04%)	125 (32.05%)	88 (43.78%)	3.503	0.005
Very severe	127 (21.49%)	65 (16.67%)	62 (30.85%)	5.120	<0.001
Social needs					
Mild	233 (39.42%)	152 (38.97%)	81 (40.30%)		
Moderate	280 (47.38%)	181 (46.41%)	99 (49.25%)	0.931	0.726
Severe	67 (11.34%)	51 (13.08%)	16 (7.96%)	0.616	0.189
Very severe	11 (1.86%)	6 (1.54%)	5 (2.49%)	1.502	0.489
Global status					
Mild	2 (0.34%)	2 (0.51%)			

Continued

Table 1 Continued

Variable	1 Year mortality			Univariate logistic ORs	Univariate logistic p values
	All patients n=591	Alive n=390 (66%)	Dead n=201 (34%)		
Moderate	86 (14.55%)	76 (19.49%)	10 (4.98%)		
Severe	474 (80.20%)	306 (78.46%)	168 (83.58%)	4.220	<0.001
Very severe	29 (4.91%)	6 (1.54%)	23 (11.44%)	29.082	<0.001

Dependent variable: 1 year mortality. Scale ranges—Barthel: 0–100, Lawton and Brody:0–8.
COPD, chronic obstructive pulmonary disease; GMA, adjusted morbidity group.

and chronic renal failure (67.66%). On the other hand, asthma (19.4) and cirrhosis (6.47%) are less common.

With respect to multivariate modelling (table 2), variables found to be independently associated to death and included into the final prediction model (Model 1) were the Barthel Scale, creatinine value and patient global status. When considering the degree of dependency as a measure of functional status (Model 2) rather than the Barthel Scale, the existence of pressure ulcers was also fit into the final model. However, the model that included the Barthel Scale was considered the most appropriate model. Some additional basic models are included in a online supplementary appendix.

The Hosmer-Lemeshow calibration test returned a p value of 0.761, and the calibration plot is presented in figure 1. The model discrimination capability, measured as the area under the ROC curve, is 0.751. Regarding validation, the cross-validation method yielded an AUC of 0.744 (95% CI 0.701 to 0.788), and when Bootstrapping was used, the AUC was 0.751 (95% CI 0.711 to 0.791). The percentage of correctly classified patients is 72.08%, with a sensitivity of 57.21% and a specificity of 79.74%.

A graphical calculation instrument, a nomogram, is provided in figure 2. This tool synthesises the results from the final multivariate model and provides a way to estimate individual probabilities of dying. The nomogram uses the observed values for each variable of interest and produces an estimated probability of death for each patient through a set of interconnected scales.

Consider the following example (figure 3) on how to use the provided nomogram. We estimate the probability of death for a patient with the following observed values for identified predictors—Barthel Scale: 15; creatinine: 2.86 mg/dL; global status: severe. These values correspond to the following risk scores—Barthel Scale ≈ 6.2 points; creatinine ≈ 3.3 points; severe global status ≈ 4.2. The total risk score for this patient is 6.2+3.3+4.2=13.7, which corresponds approximately to a probability of dying during 1 year follow-up ≈ 67%.

The nomogram can be used to apply the model estimated above to all patients at patient enrolment, and at any time thereafter if patient conditions change or regular reassessments are scheduled. New data collection for variables included into the final prediction model would be required when reassessments are performed.

DISCUSSION

This study developed and validated a mortality prediction model that estimates risk of death and identifies independent predictors of death for a population of patients with non-cancer multiple chronic conditions with a level of discrimination power equivalent to other mortality prediction models with similar sample sizes and mortality rates.

Table 2 Multivariate logistic regression to 1 year mortality

Variable	Model 1		Model 2	
	ORs (95% CI)	P value	ORs (95% CI)	P value
Barthel Scale	0.979 (0.972 to 0.987)	0.000	–	–
Degree of dependency II: severe	–	–	2.343 (1.203 to 4.565)	0.016
Degree of dependency III: great dependency	–	–	2.642 (1.465 to 4.764)	0.001
Creatinine (mg/dL)	1.284 (1.022 to 1.613)	0.032	1.290 (1.030 to 1.616)	0.027
Presence of pressure ulcers	–	–	1.572 (1.048 to 2.358)	0.029
Severe global status	3.573 (1.752 to 7.286)	0.000	3.829 (1.874 to 7.823)	0.000
Very severe global status	20.699 (6.408 to 66.855)	0.000	21.846 (6.797 to 70.215)	0.000
Constant	0.322 (0.140 to 0.737)	0.007	0.057 (0.026 to 0.126)	0.000
AUC	0.751		0.737	

Dependent variable: 1 year mortality.
AUC, area under the curve.

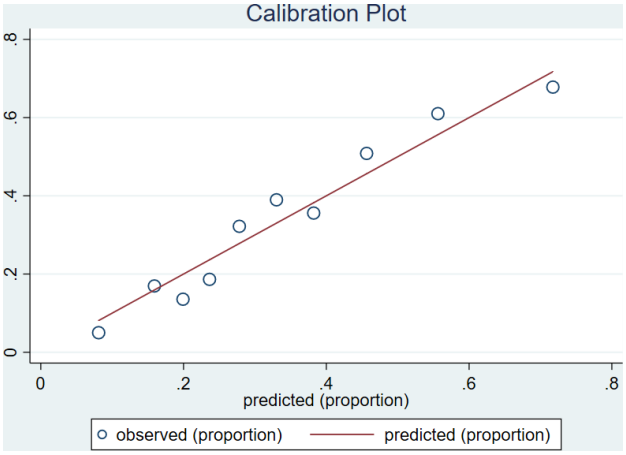

Figure 1 Model calibration plot.

Several patient features were recognised as relevant prognostic indicators of death. These include functional status, renal deterioration, pressure ulcers and patient global status, which measures three different dimensions: clinical severity, nursing needs and social needs.

Concerning functional status, the Barthel Scale was a better predictor in comparison to the degree of dependency in AUC terms. Besides, whereas the Barthel score can be easily calculated, the degree of dependency requires an award by a qualified committee,[16] making the proceeding slow and time consuming. Therefore using the model that includes the Barthel Scale is not only better when considering AUC, but also simpler, faster and easier to use in clinical settings.

Global status was also preferred to the individual inclusion of clinical severity, nursing needs or social needs variables on the basis of higher AUC values, but also because global status is a combination of all the former, and therefore taking all three dimensions into account at the same time.

The recognition of these predictors constitutes the starting process of early identification of palliative patients' needs.[15] Our model helps in detecting those needs and guiding transitions towards end-of-life care.

However, mortality prediction presents a still image of patient prospects. Frequent reassessments should monitor changing progression of each patient's needs. Patient decline would be observed, and care strategies would be tailored to changing needs.

Among study limitations, cognitive status variables were not included in the analysis. In our sample, cognitive status variables such as the Mini-Mental State Examination are being collected predominantly in those patients diagnosed with dementia, resulting in very high missing data rates (73%) that would make results unreliable and biassed. Therefore, although these variables were collected, we decided not to include them in the analysis. Furthermore, we lacked quality of life data, for instance the EQ-5D, which might have improved risk prediction and helped to achieve higher AUC values. To our knowledge, no other mortality prediction models that focus on patients with chronic have included such variables.

Some issues can affect transferability of the study. Some predictor variables may not be available in certain contexts, as it is the case for professional-rated variables, that may be registered in different ways. Degree of dependency is a variable that is registered according to Spanish law, representing an additional reason to use the model that includes the Barthel score as a predictor. Even so, using degree of dependency is still worth including as it shows the effect of pressure ulcers in Model 2. GMA score is also widely available in Spain but not in other countries, although the top 5% risks of the population can still be identified using other stratification tools. As a final point, the model was not validated using an external dataset, but using internal validation techniques instead.

In relation to the discrimination ability of our model, a systematic review by Siontis *et al*[27] showed that mortality prediction models with sample sizes between 288 to 810 participants had an AUC of 0.76 on average, and if mortality rates were above 33%, mean AUC values were 0.73. Given these data, we considered that our model had a good degree of

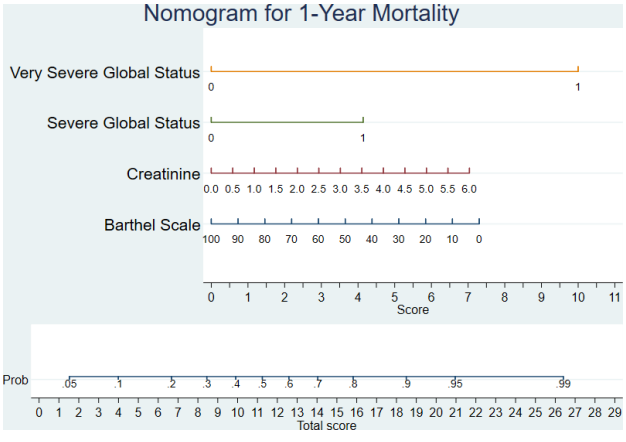

Figure 2 Nomogram for graphical risk score calculation.

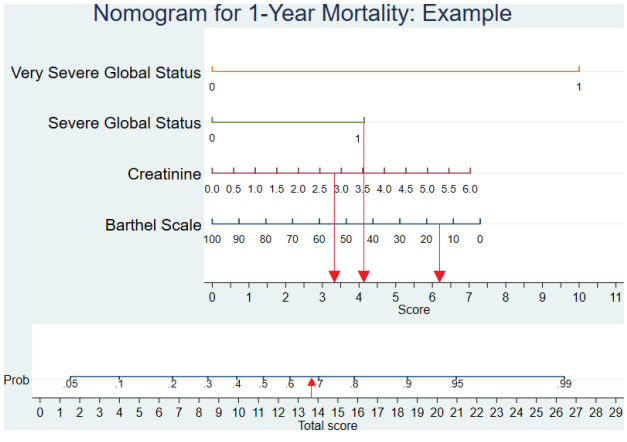

Figure 3 Example of nomogram risk score calculation.

discrimination ability; especially taking into account the specific characteristics of patients with multiple chronic conditions such as entry–re-entry life trajectories, which make death difficult to predict.

Similar mortality prediction models for patients with chronic diseases have been carried out in the past, however these included patients with cancer,[28 29] or they included patients with no comorbidities.[29–31]

Despite these differences in study populations, functional status and the Barthel Scale in particular was identified as a key indicator of death across the literature, confirming the results presented above.[28 31] Gené Badia *et al*[31] also confirmed that pressure ulcers have a significant role in end-of-life. These studies also found that nutritional values[15] and dementia[28] were strong predictors of death. However, we only found serum albumin and dementia significant at the univariate analysis.

Our results showed that age is related to death, but not as an independent predictor. The reason for this result is that age and functional status were closely correlated between them, and thus only functional status was included into the final model. While some authors confirmed our findings,[29] others included age in their models.[28]

Concerning GMA score, Dueñas-Espín *et al*[18] found that it is a good predictor in explaining healthcare expenditure and resource utilisation, yet it does not perform as well when explaining mortality. These judgments are supported by our results.

No standard definition of patients with multiple chronic conditions is given in the literature, with some authors taking into consideration patients with two or more chronic conditions,[3 28] and others[32] (including us) defining them as patients with three or more simultaneous conditions. Moreover, the selection of clinical conditions included in analysis varies from study to study. The programme considered in this study only allows enrolment of patients with three or more predefined chronic illnesses, according to a previous segmentation based on number of comorbidities, severity and age.[20] Patients who do not meet these criteria are not enrolled in the programme, leaving a considerable amount of patients with less or other non-cancer chronic conditions out of it. Since these patients fall out of the scope of action of the programme, we do not have data to estimate how well the model predicts mortality on them. This remains as a future area of research.

CONCLUSION

With the purpose of providing tools for the identification of patients who would benefit from non-cancer palliative care rather than integrated care programmes, a mortality predictive model has been developed in a population of patients with multiple chronic conditions. Results have been translated into a nomogram to enhance their applicability in clinical practices. In this way, probability of death can be estimated for each individual to allow flagging of potential palliative care patients.

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