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DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN OBSERVATIONAL STUDY.

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What is already known on this topic

Delirium is a common and serious disorder associated with morbidity and mortality in patients admitted to acute medical wards.

The rules published so far have limited applicability in a busy medicine unit.

What this study adds

A new clinical prediction rule for delirium has been developed and validated.

This is a simple clinical prediction rule based on easily measurable variables.

This rule may facilitate early identification of high risk patients and target early initiation of preventive measures.

ABSTRACT

Objectives: To develop and validate a simple clinical prediction rule, based on variables easily measurable at admission, to identify patients at high risk of developing delirium during their hospital stay on an internal medicine ward.

Design: Prospective study of two cohorts of patients admitted between May 1st and June 30th 2008 (derivation cohort), and between May 1st and June 30th 2009 (validation cohort).

Setting: A tertiary hospital in Donostia-Gipuzkoa (Spain)

Participants: 397 patients participated in the study. The mean age and prevalence of delirium were 75.9 years and 13% respectively in the derivation cohort, and 75.8 years and 25% in the validation cohort.

Main outcome measures: The predictive variables analysed and finally included in the rule were: being aged 85 years old or older, being dependent in 5 or more activities of daily living, and taking 2 or more psychotropic drugs (antipsychotics, benzodiazepines, antidepressants, anticonvulsant, and/or antidementia drugs). The variable of interest was delirium as defined by the short Confusion Assessment Method, which assesses four characteristics: acute onset and fluctuating course, inattention, disorganised thinking, and altered level of consciousness.

Results: We developed a rule in which the individual risk of delirium is obtained by adding 1 point for each criterion met (age≥85, high level of dependence, and being on psychotropic medication). The result is considered positive if the score is ≥ 1. The rule accuracy was: sensitivity = 93.4% (95% CI: 85.5-97.2),

specificity = 60.6% (95% CI: 54.1-66.8), PPV = 44.4% (95% CI: 36.9-52.1), and NPV = 96.5% (95% CI: 92-98.5). The area under the ROC curve was 0.85 for the validation cohort.

Conclusions: The presence or absence of any of the three predictive factors (age≥85, high level of dependence, and psychotropic medication) allowed us to classify patients on internal medicine wards according to the risk of developing delirium. The simplicity of the variables in our clinical prediction rule means that the data collection required is feasible in busy medicine units.

Introduction:

Delirium, also referred to as acute confusional state, is an acute disturbance of attention and cognition with a fluctuating course that often appears in hospitalised patients. Between 10% and 30% of patients admitted to general hospitals develop delirium,[1-3] with a prevalence of up to 60% among frail elderly patients.[4] It is a serious complication that increases mortality[5] and reduces the functional status of patients,[6] as well as increasing the length of hospital stays[7-8] and rates of readmission.[9] While the pathophysiology of delirium remains poorly understood, multiple risk factors have been identified.[10] These can be classified into two groups: factors that increase baseline vulnerability (presence of dementia, cerebrovascular accident, Parkinson´s disease, old age, and sensory impairment, among others);[11] and those that may be a trigger (such as polypharmacy, infection, and dehydration).[12-14]

Various interventions to improve modifiable variables have been found effective in preventing the occurrence of delirium.[15-18] Therefore, the identification of patients at high risk of developing delirium is particularly important.[19]

Clinical prediction rules are useful tools for classifying patients at different levels of risk.[20] Other authors proposed a rule to predict the risk of developing delirium[21] for use in patients admitted due to clinical worsening of their condition, but its use has not become widespread in our setting since it requires variables that are difficult to measure on admission (Mini-Mental State Examination score, and visual acuity, among others).

The objective of this study was to derive and validate a simple clinical prediction rule, based on variables that are easily measurable and are often routinely taken on admission, to identify patients at high risk of developing delirium during their hospital stay on an internal medicine ward.

The identification of these patients will allow us to introduce the necessary preventative measures.

Methods

Design

To develop the clinical prediction rule we assessed a prospective cohort of consecutive patients admitted in four internal medicine wards. Subsequently, we assessed a different prospective cohort of consecutive patients to validate the rule.

Patients

The derivation cohort was 397 consecutive patients aged 18 years or over, of both sexes, who were admitted to any of four internal medicine wards at Donostia Hospital between May 1st 2008 and June 30th 2008, and we used no other exclusion criteria. The following year, between May 1st 2009 and June 30th 2009, we recruited the validation cohort on the same basis: 302 consecutive patients aged 18 or over, of both sexes, who were admitted to any of the same four internal medicine wards at the hospital.

Assessment of delirium

We defined delirium using the short version of the Confusion Assessment Method (22), a short form for assessing confusion. This diagnostic algorithm assesses four characteristics: 1) acute onset and fluctuating course, 2) inattention, 3) disorganised thinking, and 4) altered level of consciousness. The

diagnosis of delirium required the presence of 1) and 2), and either 3) or 4) (or both). This assessment was performed by two independent researchers, when it was considered that patients were ready for discharge, after analysis of any relevant data in their medical record and nursing report. Disagreements were resolved by consensus with a third researcher. All these evaluators were blinded to the potential predictive variables.

Potential predictors

The potential predictive variables for delirium were selected after a systematic review of the literature[10-14 23-25]. We sought to identify variables that were easy to measure and are often routinely recorded on admission to these wards.

The following variables were selected and measured on admission: age (years), sex, systolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/minute), axillary temperature (°C), oxygen therapy (no: not used; and yes: oxygen with nasal cannula, mask, and/or oxygen at home), fluid therapy, presence of urinary catheter, level of consciousness (normal: alert; or altered: drowsiness, unresponsiveness to voice, unresponsiveness to pain, and/or generally unresponsive), diagnosis of infection at admission (respiratory, urinary or other types of infections; or no infection: any other cause of admission), admission in the previous year, admission in the previous month, hearing impairment (use of a hearing aid, or deafness reported by the patient or caregiver), vision impairment (regular use of glasses or reduction in visual acuity reported by the patient or caregiver), and dementia (in a medical report or reported by the caregiver). In addition, blood tests were taken on admission to

measure the following: haematocrit (%), levels of urea (mg/dl), creatinine (mg/dl), sodium (mEq/l), potassium (mEq/l), and glucose (mg/dl), as well as white blood cell (10e3/µl) and neutrophil (10e3/µl) counts. Lastly, certain characteristics of patients prior to admission were also assessed: level of dependence for activities of daily living (personal hygiene and grooming, dressing and undressing, getting onto or off toilet, ambulation, bowel and bladder control, and self-feeding) as dichotomous variables (dependent; independent); presence of pressure ulcers, and excess alcohol intake (>60 g/ethanol/day), as well as use of certain types of medication: benzodiazepines, antidepressants, antidementia drugs, antipsychotics, anti-Parkinson's drugs, or anticonvulsants.

Statistical analysis

A descriptive analysis was carried out, based on the calculation of means and standard deviations for continuous variables, and absolute or relative frequencies as percentages for categorical variables. Subsequently, some continuous variables were dichotomised using the median value.

Sample size

Assuming a prevalence of delirium at admission of 10%, it was calculated that we needed 10 patients with delirium for each variable included in the model, with the intention that the model should be as parsimonious as possible.

Comparison between derivation and validation cohorts

We compared the characteristics of patients in the derivation cohort with those in the validation cohort using the Student's t-test for continuous variables and the Chi square test for ordinal and dichotomous variables.

Derivation of the prediction rule

The characteristics of patients who developed delirium were compared with those of patients who did not, again using the Student's t-test or the Chi square test as appropriate. A p-value <0.25 was taken to indicate potentially predictive variables and those meeting this criteria were included in the multivariate model. Then, using a stepwise logistic regression model we selected the terms (predictive variables) to be included in the final model. The criteria for entry in the model and for removal were $p \leq 0.05$ and $p \geq 0.10$ respectively. The Hosmer Lemeshow test was performed to assess the goodness of fit of this model.

We note that we also explored selecting variables for an alternative prediction rule by recursive partitioning. However, as the performance of this rule was poorer than that of the rule obtained by logistic regression, we decided to report exclusively the data concerning the rule derived using the latter method.

Validation cohort and model performance

The clinical prediction rule was applied to the validation cohort. We report the incidence of delirium as a function of score on the rule and the ORs using the

lowest risk category as the reference. The performance of the rule in the two cohorts was explored using ROC curve analysis.

To assess the diagnostic accuracy of the rule, we constructed a 2x2 table for calculation of the following: sensitivity, specificity, and positive and negative predictive values. The 95% confidence intervals of these indicators were also calculated assuming a binomial distribution.

We used SPSS 19.0 and MedCalc for all the analysis.

Results

In the validation cohort, 13% of patients (52 out of 397) developed delirium, and in the derivation cohort the prevalence was 25.2% (76 out 302). Table 1 summarises baseline characteristics of the derivation and validation cohorts. Patients included in our study were elderly (76.4±13.3 years old) and slightly more than half were women (52%, 362 out of 699). The derivation and validation cohorts were similar in some respects, namely, age, sex, mean length of stay, and types of medication. On the other hand, patients in the validation cohort were significantly more dependant in certain activities of daily living: personal hygiene and grooming, dressing and undressing, and getting onto or off toilet.

Tables 2 to 6 report the results of the univariate analysis in which the risk factors were compared between patients who developed delirium and those who did not within the derivation cohort. Those who developed delirium were significantly older and had slightly higher respiratory rates, but there were no significant differences in blood test results.

Age was dichotomised using a cut-off of 85 years, a value that was found to have a sensitivity of 85% and a specificity of 56% for delirium by the ROC curve analysis. We found that the risk of delirium associated with the types of medication considered was similar for all except antipsychotic drugs, for which the risk was twice as high. Accordingly, the medication data was coded according to the number of different drugs patients were taking at admission with each antidepressant, antidementia, or anticonvulsant drug contributing equally, while antipsychotic drugs were weighted by a factor of two. The

activities of daily living data were also dichotomised with a cut-off of reported impairments in five activities.

The scores for the clinical prediction rule were assigned on the basis of regression coefficients obtained in the logistic regression model (Table 7). One point was given to patients older than 85 years, to those who had 2 or more points in the variable drugs, and to those with impairments in five or more of the activities of daily living considered. Therefore, the total score for the rule ranged between 0 and 3.

Table 9 and Figures 1 and 2 describe the performance of the rule in the derivation and validation cohorts. In both cohorts, we observed higher rates of delirium associated with higher scores on the rule, the model having a good predictive power for the validation cohort (area under the ROC curve, AUC = 0.85). In contrast with what would be expected, the values obtained in the validation cohort are better than those obtained in the derivation cohort, and this is probably related to the higher prevalence of delirium in validation group.

In particular, Table 9 lists the sensitivity (Se) and specificity (Sp), as well as the positive and negative predictive values (PPVs and NPVs) obtained when the rule was dichotomised as negative (a score of 0) or positive (as score of ≥1). For the validation cohort, the Se, Sp, NPV, and PPV were 93.4%, 60.6%, 96%, and 44% respectively.

DISCUSSION

In this prospective study, we identified three independent predictive factors for delirium: being 85 years old or older, being dependent in five or more activities of daily living (of the six considered), and taking psychotropic drugs (antipsychotics, benzodiazepines, antidepressants, anticonvulsants, and/or antidementia drugs). With these factors we developed a clinical prediction rule in which an individual risk score for delirium is obtained by adding 1 point for each of the factors present. Applying this rule, patients are classified as positive if they have a total score of 1 or more. Selecting the cut-off point for the highest sensitivity, the accuracy of the rule was: Se=93.4% (95% CI 85.5 to 97.2), Sp= 60.6% (95% CI 54.1 to 66.8), PPV = 44.4% (95% CI 36.9 to 52.1), and a NPV = 96.5% (95% CI 92 to 98.5). The AUCs were 0.77 and 0.85 in the derivation and validation cohorts, respectively.

In the derivation cohort, 13% of patients developed delirium, while the prevalence was somewhat higher, 25%, in the validation cohort. Patients were elderly (mean ages in the derivation and validation cohorts were 75.9 +/- 13.3 years and 76.8 +/- 13.3 years respectively), and there were slightly more women (52%). The mean length of hospital stay was 8 +/- 5.8 days and overall mortality was 5%.

There are multiple factors for the development of delirium, the predisposing and triggering factors being well defined. The predisposing factors are mostly related to degenerative brain disease (dementia, arteriosclerosis, Parkinson´s disease, and depression).[10 11] On the other hand, there are a diverse range of

triggering factors, in particular, medication, the presence of infection, surgery, metabolic disorders, and water-electrolyte imbalances, among others.[13 14 23-25]

In the present study, we have only explored variables that are readily available on admission, in order to use the predictive rule at that stage and be able to introduce preventative measures immediately in high-risk patients. These would include trying to avoid triggering factors for the development of delirium (such as changes of room/ward, unnecessary catheterisation, inadequate oral hydration, and polypharmacy).

Interestingly, the factors found to be good predictors for the development of delirium in our study (age≥85, high level of dependence, and being on psychotropic medication), to some extent, indirectly reflect the severity of the organic brain damage in patients with delirium.

Another predictive rule for delirium in this type of patients has been published (21) but showed a significantly lower performance than that we obtained (AUC = 0.66 [0.55-077] vs. AUC=0.85 [0.80-0.90] with our rule). Further, in our opinion, it is also more difficult to apply than the rule we propose. The simplicity of the variables included in our rule makes data collection a feasible task for busy healthcare units.

Between 10% and 60% of patients admitted to hospital develop delirium, depending on the type of patient, the prevalence in frail elderly patients being at the top of this range. In our study, it was 13% and 25% in the derivation and validations cohorts, respectively. Delirium is well known to be difficult to diagnose and a wide range of instruments have been developed to help detect the condition (26,27). We used the Confusion Assessment Method[22] that has a

sensitivity of 96% (95% CI 80-100%) and a specificity of 93% (95% CI 84-100%). In our study, the doctors in charge of the diagnosis of delirium were specialists in internal medicine, with considerable training and experience in the management of this type of patients, any differences being resolved by consensus with a third specialist. We note, however, that the diagnoses of delirium were not confirmed by a psychiatrist. This may partially explain the low prevalence of delirium in our patients, that is, it may be that only the most clinically striking cases, those which required pharmacological treatment, were recognised.

The association between delirium and an increase of morbidity and mortality[5 6 9] is well known, as are the effectiveness of preventive measures to avoid the development of the disease.[15-18] The use of the proposed predictive rule would allow us to classify around half of our inpatients (53%) as high-risk. Taking preventative measures in this high risk group, up to 93.4% of those who developed delirium in our study would have been covered by the measures and might not have then developed the condition.

It would interesting for the clinical predictive rule we propose to be validated in other cohorts of frail elderly patients with worsening of multiple medical conditions to check its external validity.

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CONTRIBUTORS: JM, AB, JIE and IU participated in the design of the study. JM, AB, IB, XG, CA and NL collected all data. JIE and IU carried out the statistical analysis. JM, IU and JIE drafted the manuscript. All authors approved the final version to be published. IU and JM are the guarantors.

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ETHICAL APPROVAL: The design was evaluated and then approved by the Clinical Research Ethics Committee of the Gipuzkoa Health region.

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Table 1 Characteristics of patients in the derivation and validation cohorts

Characteristics	Derivation cohort (n=397)	Validation cohort (n= 302)	p
Mean age (SD)	75.9 (13.3)	76.8 (13.3)	N.S
Mean length of stay (SD)	8.4 (5.8)	8 (6.1)	N.S
Women (%)	197 (49.6)	165 (54.3)	N.S
Medication (%)			
Benzodiazepines	162 (40.8)	134 (44.4)	N.S
Antidepressants	75 (18.9)	74 (24.5)	N.S
Antidementia drugs	20 (5)	11 (3.6)	N.S
antipsychotics	24 (6)	21 (7)	N.S
Anti-Parkinson´s agents	13 (3.3)	6(2)	N.S
Anticonvulsants	20 (5)	16 (5.3)	N.S
Dependence in activities of daily living (%)			
Personal hygiene and grooming	155 (39)	171 (56.6)	<0.05
Dressing and undressing	155 (39)	174 (57.6)	<0.05
Getting onto or off toilet	146 (36.8)	161 (53.3)	<0.05
Ambulation	163 (41.1)	166 (55)	<0.05
Bowel and bladder control	139 (35)	122 (40.4)	N.S
Self-feeding	109 (27.5)	102 (33.8)	N.S

Table 2 Derivation cohort: univariate analysis of patient clinical variables considered potential risk factors for delirium at admission. Mean (SD)

Variables	Delirium	No delirium	p
Age (years)	83.83 (9.8)	74.75 (13.4)	0.000
Blood pressure (mmHg)	127.5 (27.1)	132.3 (26.5)	0.22
Respiratory rate (breaths/min)	27.92 (9.6)	24.42 (6.6)	0.001
Heart rate (beats/min)	86.6 (23.8)	84.06 (22.5)	N.S
Body temperature (°C)	36.7 (0.7)	36.7 (0.8)	N.S
Women (%)	26 (50)	171 (49.6)	NS
Excess alcohol intake (%)	2 (3.8)	19 (5.5)	NS
Mean length of stay in hospital (days)	9.3 (6.6)	8.3 (5.6)	N.S
Admission in previous year (%)	26 (50)	152 (44.1)	NS
Admission in previous month (%)	8(15.1)	45 (84.9)	NS

Table 3 Derivation cohort: univariate analysis of patient blood test results at admission. Mean (SD)

Variables	Delirium	No delirium	p
Haematocrit (%)	39.31 (7.6)	37.42 (6.5)	0.058
Urea (mg/dl)	62.3 (31.6)	60.3 (40.7)	N.S
Creatinine (mg/dl)	1.14 (0.5)	1.25 (0.9)	N.S
Sodium (mEq/l)	138.5 (5.6)	173.9 (5.5)	N.S
Potassium (mEq/l)	5.2 (6.9)	4.8 (0.7)	N.S
Glucose (mg/dl)	140.1 (66.3)	140.8 (78.8)	N.S
White blood cells (10e3/µl)	12.1 (12.2)	10.1(4.7)	N.S
Neutrophils (10e3/µl)	9.8 (8.5)	10.8 (14.8)	N.S

Table 4 Derivation cohort: univariate analysis of patient medication prior to admission.

Variables	Delirium	No delirium	p
Antidepressants	16 (30.8)	59 (17.1)	0.023
Antidementia drugs	5 (9.6)	15 (4.3)	0.16
Antipsychotics	8 (15.4)	16 (4.6)	0.007
Anticonvulsants	5 (9.6)	15 (4.3)	0.16
Benzodiazepines	23 (44.2)	139 (40.3)	NS

Table 5 Derivation cohort: variables characterising patient status on admission

Variables	Delirium	No delirium	p
Urinary catheter	13 (25)	37(10.7)	NS
Fluid therapy	29 (55.8)	124 (35.9)	0.009
Vision impairment	36 (69.2)	192 (55.7)	0.072
Hearing impairment	9 (17.3)	87 (25.2)	NS
Oxygen therapy	32 (61.5)	202 (58.6)	NS
Pressure ulcers	3 (5.8)	25 (7.3)	NS
Level of consciousness	5 (21.7)	18 (78.3)	0.20
Dementia	18 (34.6)	49 (14.2)	0.001
Infection	28 (53.8)	141(40.8)	0.097

Table 6 Derivation cohort: univariate analysis of patient activities of daily living

Variables	Delirium	No delirium	p
Impaired personal hygiene and grooming	39 (75)	116 (33.6)	0.0001
Impaired dressing and undressing	38 (73.1)	117 (33.9)	0.0001
Impaired getting onto or off toilet	36 (69.2)	110 (31.9)	0.001
Impaired ambulation	38 (73.1)	125 (36.2)	0.001
Impaired bowel and bladder control	36 (69.2)	103 (29.9)	0.001
Impaired self-feeding	31 (59.6)	78 (22.6)	0.000
Dependence in ≥ 5 activities	36 (69.2)	87(25.2)	0.0001

Table 7 Variables included in the logistic regression model

Variables	B	SE	Wald	Degrees of freedom	Sig.	Exp(B)
Age [1]	1.381	0.349	15.664	1	0.000	3.978
DADLs[2]	1.397	0.350	15.924	1	0.000	4.042
Drugs[3]	1.515	0.443	11.715	1	0.001	4.547
Constant	-3.234	0.295	120.122	1	0.000	0.039

[1] Age: > 85 years old

[2] DADLs: Dependence in 5 or more activities of daily livings

[3] Drugs: total of 2 or more points for drugs taken on admission where antidepressants, antidementia drugs, and anticonvulsants score 1 point each, and antipsychotics score 2 points

Table 8 Logistic regression model

Group	Points on the prediction rule	Incidence of delirium (%)	OR	AUC (IC 95%)
Derivation cohort (n=397)				0.77 (0.73-0.82)
	0	9/219 (4)	Reference	
	1	16/116 (14)	3.7 (1.5-8.7)	
	≥2	27/62 (43)	18 (7.8-41.5)	
Validation cohort (n=302)				0.85 (0.8-0.88)
	0	5/142 (3.5)	Reference	
	1	18/77 (23)	8.3 (2.9-23.6)	
	≥2	53/83 (64)	48.4 (17.8-131.4)	

Table 9 A 2 X 2 table for the validation cohort

Cut-off point	Delirium	No delirium	Total
0 (negative)	5	137	142
≥1 (positive)	71	89	160
	76	226	302

Sensitivity = 93.4%, 95% CI 85.5 to 97.2

Specificity = 60.6%, 95% CI 54.1 to 66.8

PPV = 44.4%, 95% CI 36.9 to 52.1

NPV = 96.5%, 95% CI 92 to 98.5

Figure 1: ROC curve for the derivation cohort

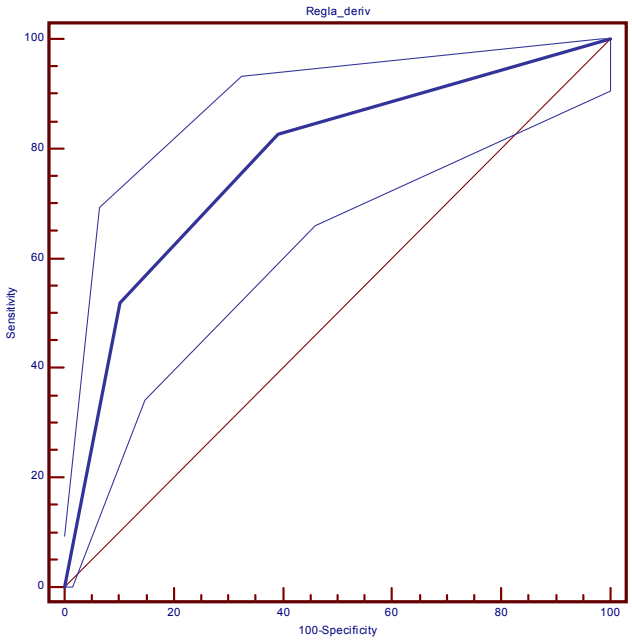
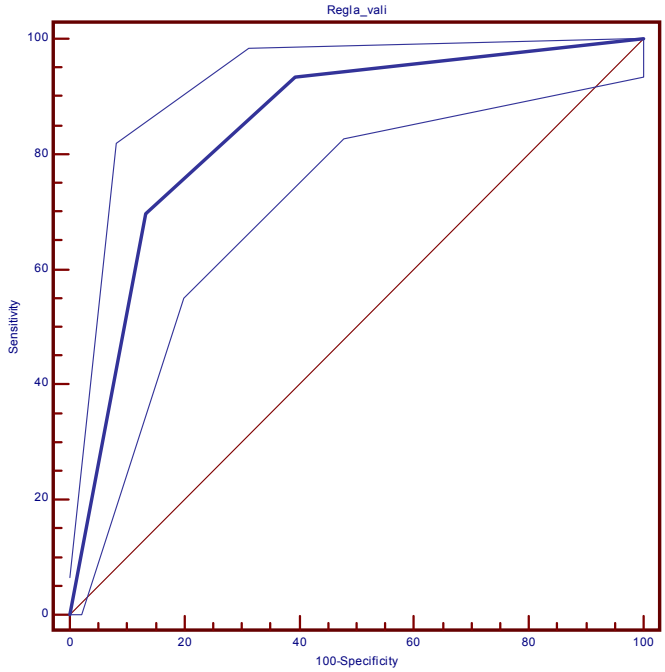


Figure 2: ROC curve for the validation cohort



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN OBSERVATIONAL STUDY.

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Secondary Subject Heading:	Neurology
Keywords:	Delirium, clinical prediction rule, elderly

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DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN OBSERVATIONAL STUDY.

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What is already known on this topic

Delirium is a common and serious disorder associated with morbidity and mortality in patients admitted to acute medical wards.

The rules published so far have limited applicability in a busy medicine unit.

What this study adds

A new clinical prediction rule for delirium has been developed and validated.

This is a simple clinical prediction rule based on easily measurable variables.

This rule may facilitate early identification of high risk patients and target early initiation of preventive measures.

ABSTRACT

Objectives: To develop and validate a simple clinical prediction rule, based on variables easily measurable at admission, to identify patients at high risk of developing delirium during their hospital stay on an internal medicine ward.

Design: Prospective study of two cohorts of patients admitted between May 1st and June 30th 2008 (derivation cohort), and between May 1st and June 30th 2009 (validation cohort).

Setting: A tertiary hospital in Donostia-Gipuzkoa (Spain)

Participants: 397 patients participated in the study. The mean age and prevalence of delirium were 75.9 years and 13% respectively in the derivation cohort, and 75.8 years and 25% in the validation cohort.

Main outcome measures: The predictive variables analysed and finally included in the rule were: being aged 85 years old or older, being dependent in 5 or more activities of daily living, and taking 2 or more psychotropic drugs (antipsychotics, benzodiazepines, antidepressants, anticonvulsant, and/or antidementia drugs). The variable of interest was delirium as defined by the short Confusion Assessment Method, which assesses four characteristics: acute onset and fluctuating course, inattention, disorganised thinking, and altered level of consciousness.

Results: We developed a rule in which the individual risk of delirium is obtained by adding 1 point for each criterion met (age≥85, high level of dependence, and being on psychotropic medication). The result is considered positive if the score is ≥ 1. The rule accuracy was: sensitivity = 93.4% (95% CI: 85.5-97.2),

specificity = 60.6% (95% CI: 54.1-66.8), PPV = 44.4% (95% CI: 36.9-52.1), and NPV = 96.5% (95% CI: 92-98.5). The area under the ROC curve was 0.85 for the validation cohort.

Conclusions: The presence or absence of any of the three predictive factors (age≥85, high level of dependence, and psychotropic medication) allowed us to classify patients on internal medicine wards according to the risk of developing delirium. The simplicity of the variables in our clinical prediction rule means that the data collection required is feasible in busy medicine units.

Introduction:

Delirium, also referred to as acute confusional state, is an acute disturbance of attention and cognition with a fluctuating course that often appears in hospitalised patients. Between 10% and 30% of patients admitted to general hospitals develop delirium,[1-3] with a prevalence of up to 60% among frail elderly patients.[4] It is a serious complication that increases mortality[5] and reduces the functional status of patients,[6] as well as increasing the length of hospital stays[7-8] and rates of readmission.[9] While the pathophysiology of delirium remains poorly understood, multiple risk factors have been identified.[10] These can be classified into two groups: factors that increase baseline vulnerability (presence of dementia, cerebrovascular accident, Parkinson´s disease, old age, and sensory impairment, among others);[11] and those that may be a trigger (such as polypharmacy, infection, and dehydration).[12-14]

Various interventions to improve modifiable variables have been found effective in preventing the occurrence of delirium.[15-18] ~~Therefore,~~Therefore; the identification of patients at high risk of developing delirium is particularly important.[19]

Clinical prediction rules are useful tools for classifying patients at different levels of risk.[20] Other authors proposed a rule to predict the risk of developing delirium[21] for use in patients admitted due to clinical worsening of their condition, but its use has not become widespread in our setting since it requires variables that are difficult to measure on admission (Mini-Mental State Examination score, and visual acuity, among others).

The objective of this study was to derive and validate a simple clinical prediction rule, based on variables that are easily measurable and are often routinely taken on admission, to identify patients at high risk of developing delirium during their hospital stay on an internal medicine ward.

The identification of these patients will allow us to introduce the necessary preventative measures.

Methods

Design

To develop the clinical prediction rule we assessed a prospective cohort of consecutive patients admitted in four internal medicine wards. Subsequently, we assessed a different prospective cohort of consecutive patients to validate the rule.

Patients

The derivation cohort was 397 consecutive patients aged 18 years or over, of both sexes, who were admitted to any of four internal medicine wards at Donostia Hospital between May 1st 2008 and June 30th 2008, and we used no other exclusion criteria. The following year, between May 1st 2009 and June 30th 2009, we recruited the validation cohort on the same basis: 302 consecutive patients aged 18 or over, of both sexes, who were admitted to any of the same four internal medicine wards at the hospital. The consent was obtained from the study participants and all patients gave their consent to participate in the study.

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Assessment of delirium

We defined delirium using the short version of the Confusion Assessment Method, ~~(22)~~[22], a short form for assessing confusion. This diagnostic algorithm assesses four characteristics: 1) acute onset and fluctuating course, 2)

inattention, 3) disorganised thinking, and 4) altered level of consciousness. The diagnosis of delirium required the presence of 1) and 2), and either 3) or 4) (or both). This assessment was performed by two independent researchers, when it was considered that patients were ready for discharge, after analysis of any relevant data in their medical record and nursing report. Disagreements were resolved by consensus with a third researcher. All these evaluators were blinded to the potential predictive variables selected for the study.

Potential predictors

The potential predictive variables for delirium were selected after a systematic review of the literature[10-14 23-25]. We sought to identify variables that were easy to measure and are often routinely recorded on admission to these wards.

The following variables were selected and measured on admission: age (years), sex, systolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/minute), axillary temperature (°C), oxygen therapy (no: not used; and yes: oxygen with nasal cannula, mask, and/or oxygen at home), fluid therapy, presence of urinary catheter, level of consciousness (normal: alert; or altered: drowsiness, unresponsiveness to voice, unresponsiveness to pain, and/or generally unresponsive), diagnosis of infection at admission (respiratory, urinary or other types of infections; or no infection: any other cause of admission), admission in the previous year, admission in the previous month, hearing impairment (use of a hearing aid, or deafness reported by the patient or caregiver), vision impairment (regular use of glasses or reduction in visual acuity reported by the patient or caregiver), and dementia (in a medical report or

reported by the caregiver). In addition, blood tests were taken on admission to measure the following: haematocrit (%), levels of urea (mg/dl), creatinine (mg/dl), sodium (mEq/l), potassium (mEq/l), and glucose (mg/dl), as well as white blood cell (10e3/µl) and neutrophil (10e3/µl) counts. Lastly, certain characteristics of patients prior to admission were also assessed: level of dependence for activities of daily living (personal hygiene and grooming, dressing and undressing, getting onto or off toilet, ambulation, bowel and bladder control, and self-feeding) as dichotomous variables (dependent; independent); presence of pressure ulcers, and excess alcohol intake (>60 g/ethanol/day), as well as use of certain types of medication: benzodiazepines, antidepressants, antidementia drugs, antipsychotics, anti-Parkinson's drugs, or anticonvulsants.

Statistical analysis

A descriptive analysis was carried out, based on the calculation of means and standard deviations for continuous variables, and absolute or relative frequencies as percentages for categorical variables. Subsequently, some continuous variables were dichotomised using the median value.

Sample size

Assuming a prevalence of delirium at admission of 10%, it was calculated that we needed 10 patients with delirium for each variable included in the model, with the intention that the model should be as parsimonious as possible.

Comparison between derivation and validation cohorts

We compared the characteristics of patients in the derivation cohort with those in the validation cohort using the Student's t-test for continuous variables and the Chi square test for ordinal and dichotomous variables.

Derivation of the prediction rule

The characteristics of patients who developed delirium were compared with those of patients who did not, again using the Student's t-test or the Chi square test as appropriate. A p-value <0.25 was taken to indicate potentially predictive variables and those meeting this criteria were included in the multivariate model. Then, using a stepwise logistic regression model we selected the terms (predictive variables) to be included in the final model. The criteria for entry in the model and for removal were $p \leq 0.05$ and $p \geq 0.10$ respectively. The Hosmer Lemeshow test was performed to assess the goodness of fit of this model.

We note that we also explored selecting variables for an alternative prediction rule by recursive partitioning. However, as the performance of this rule was poorer than that of the rule obtained by logistic regression, we decided to report exclusively the data concerning the rule derived using the latter method.

Validation cohort and model performance

The clinical prediction rule was applied to the validation cohort. We report the incidence of delirium as a function of score on the rule and the ORs using the

lowest risk category as the reference. The performance of the rule in the two cohorts was explored using ROC curve analysis.

To assess the diagnostic accuracy of the rule, we constructed a 2x2 table for calculation of the following: sensitivity, specificity, and positive and negative predictive values. The 95% confidence intervals of these indicators were also calculated assuming a binomial distribution.

We used SPSS 19.0 and MedCalc for all the analysis.

Results

In the validation cohort, 13% of patients (52 out of 397) developed delirium, and in the derivation cohort the prevalence was 25.2% (76 out 302). Table 1 summarises baseline characteristics of the derivation and validation cohorts. Patients included in our study were elderly (76.4±13.3 years old) and slightly more than half were women (52%, 362 out of 699). The derivation and validation cohorts were similar in some respects, namely, age, sex, mean length of stay, and types of medication. On the other hand, patients in the validation cohort were significantly more dependant in certain activities of daily living: personal hygiene and grooming, dressing and undressing, and getting onto or off toilet.

Tables 2 to 6 report the results of the univariate analysis in which the risk factors were compared between patients who developed delirium and those who did not within the derivation cohort. Those who developed delirium were significantly older and had slightly higher respiratory rates, but there were no significant differences in blood test results.

Age was dichotomised using a cut-off of 85 years, a value that was found to have a sensitivity of 85% and a specificity of 56% for delirium by the ROC curve analysis. We found that the risk of delirium associated with the types of medication considered was similar for all except antipsychotic drugs, for which the risk was twice as high. Accordingly, the medication data was coded according to the number of different drugs patients were taking at admission with each antidepressant, antidementia, or anticonvulsant drug contributing equally, while antipsychotic drugs were weighted by a factor of two. The

activities of daily living data were also dichotomised with a cut-off of reported impairments in five activities.

The scores for the clinical prediction rule were assigned on the basis of regression coefficients obtained in the logistic regression model (Table 7). One point was given to patients older than 85 years, to those who had 2 or more points in the variable drugs, and to those with impairments in five or more of the activities of daily living considered. Therefore, the total score for the rule ranged between 0 and 3.

The patients with delirium of the two cohorts scored similarly: 17% and 7% scored 0, 48% and 30% scored ≤ 1 and 85% and 85% scored ≤ 2 in the derivation and validation cohort respectively.

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Table 9 and Figures 1 and 2 describe the performance of the rule in the derivation and validation cohorts. In both cohorts, we observed higher rates of delirium associated with higher scores on the rule, the model having a good predictive power for the validation cohort (area under the ROC curve, AUC = 0.85). In contrast with what would be expected, the values obtained in the validation cohort are better than those obtained in the derivation cohort, and this is probably related to the higher prevalence of delirium in validation group.

In particular, Table 9 lists the sensitivity (Se) and specificity (Sp), as well as the positive and negative predictive values (PPVs and NPVs) obtained when the rule was dichotomised as negative (a score of 0) or positive (as score of ≥1). For the validation cohort, the Se, Sp, NPV, and PPV were 93.4%, 60.6%, 96%, and 44% respectively

DISCUSSION

In this prospective study, we identified three independent predictive factors for delirium: being 85 years old or older, being dependent in five or more activities of daily living (of the six considered), and taking psychotropic drugs (antipsychotics, benzodiazepines, antidepressants, anticonvulsants, and/or antidementia drugs). With these factors we developed a clinical prediction rule in which an individual risk score for delirium is obtained by adding 1 point for each of the factors present. Applying this rule, patients are classified as positive if they have a total score of 1 or more. ~~Selecting the cut-off point for the highest sensitivity, the accuracy of the rule was: Se=93.4% (95% CI 85.5 to 97.2), Sp= 60.6% (95% CI 54.1 to 66.8), PPV = 44.4% (95% CI 36.9 to 52.1), and a NPV = 96.5% (95% CI 92 to 98.5). The AUCs were 0.77 and 0.85 in the derivation and validation cohorts, respectively.~~

In the derivation cohort, 13% of patients developed delirium, while the prevalence was somewhat higher, 25%, in the validation cohort. Patients were elderly (mean ages in the derivation and validation cohorts were 75.9 +/- 13.3 years and 76.8 +/- 13.3 years respectively), and there were slightly more women (52%). The mean length of hospital stay was 8 +/- 5.8 days and overall mortality was 5%. There is a significant difference in the ADL variables being those from the validation cohort more dependent than the derivation cohort. All the above mention variables explain the almost two fold discrepancy in the incidence of delirium between the two cohort.

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There are multiple factors for the development of delirium, the predisposing and triggering factors being well defined. The predisposing factors are mostly related to degenerative brain disease (dementia, arteriosclerosis, Parkinson´s disease, and depression).[10 11] On the other hand, there are a diverse range of triggering factors, in particular, medication, the presence of infection, surgery, metabolic disorders, and water-electrolyte imbalances, among others.[13 14 23-25]

In the present study, we have only explored variables that are readily available on admission, in order to use the predictive rule at that stage and be able to introduce preventative measures immediately in high-risk patients. These would include trying to avoid triggering factors for the development of delirium (such as changes of room/ward, unnecessary catheterisation, inadequate oral hydration, and polypharmacy).

Interestingly, the factors found to be good predictors for the development of delirium in our study (age≥85, high level of dependence, and being on psychotropic medication), to some extent, indirectly reflect the severity of the organic brain damage in patients with delirium.

Another predictive rule for delirium in this type of patients has been published[21] ~~(21)~~ but showed a significantly lower performance than that we obtained (AUC = 0.66 [0.55-077] vs. AUC=0.85 [0.80-0.90] with our rule). Further, in our opinion, it is also more difficult to apply than the rule we propose. The simplicity of the variables included in our rule makes data collection a feasible task for busy healthcare units.

Between 10% and 60% of patients admitted to hospital develop delirium, depending on the type of patient, the prevalence in frail elderly patients being at

the top of this range. In our study, it was 13% and 25% in the derivation and validations cohorts, respectively. Delirium is well known to be difficult to diagnose and a wide range of instruments have been developed to help detect the condition.[26 27] ~~(26,27).~~ We used the Confusion Assessment Method[22] that has a sensitivity of 96% (95% CI 80-100%) and a specificity of 93% (95% CI 84-100%). In our study, the doctors in charge of the diagnosis of delirium were specialists in internal medicine, with considerable training and experience in the management of this type of patients, any differences being resolved by consensus with a third specialist. We note, however, that the diagnoses of delirium were not confirmed by a psychiatrist. This may partially explain the low prevalence of delirium in our patients, that is, it may be that only the most clinically striking cases, those which required pharmacological treatment, were recognised.

The association between delirium and an increase of morbidity and mortality[5 6 9] is well known, as are the effectiveness of preventive measures to avoid the development of the disease.[15-18] The use of the proposed predictive rule would allow us to classify around half of our inpatients (53%) as high-risk. Taking preventative measures in this high risk group, up to 93.4% of those who developed delirium in our study would have been covered by the measures and might not have then developed the condition.

It would be interesting for the clinical predictive rule we propose to be validated in other cohorts of frail elderly patients with worsening of multiple medical conditions to check its external validity.

ACKNOWLEDGEMENTS: We would like to thank all the medical and nursing staff of the Department of Internal Medicine at Donostia University Hospital for their contribution to the study.

CONTRIBUTORS: JM, AB, JIE and IU participated in the design of the study. JM, AB, IB, XG, CA and NL collected all data. JIE and IU carried out the statistical analysis. JM, IU and JIE drafted the manuscript. All authors approved the final version to be published. IU and JM are the guarantors.

COMPETING INTERESTS: All authors have completed the Unified Competing interests form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL: The design was evaluated and then approved by the Clinical Research Ethics Committee of the Gipuzkoa Health region.

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Table 1 Characteristics of patients in the derivation and validation cohorts

Characteristics	Derivation cohort (n=397)	Validation cohort (n= 302)	p
Mean age (SD)	75.9 (13.3)	76.8 (13.3)	N.S
Mean length of stay (SD)	8.4 (5.8)	8 (6.1)	N.S
Women (%)	197 (49.6)	165 (54.3)	N.S
Medication (%)			
Benzodiazepines	162 (40.8)	134 (44.4)	N.S
Antidepressants	75 (18.9)	74 (24.5)	N.S
Antidementia drugs	20 (5)	11 (3.6)	N.S
antipsychotics	24 (6)	21 (7)	N.S
Anti-Parkinson´s agents	13 (3.3)	6(2)	N.S
Anticonvulsants	20 (5)	16 (5.3)	N.S
Dependence in activities of daily living (%)			
Personal hygiene and grooming	155 (39)	171 (56.6)	<0.05
Dressing and undressing	155 (39)	174 (57.6)	<0.05
Getting onto or off toilet	146 (36.8)	161 (53.3)	<0.05
Ambulation	163 (41.1)	166 (55)	<0.05
Bowel and bladder control	139 (35)	122 (40.4)	N.S
Self-feeding	109 (27.5)	102 (33.8)	N.S

Table 2 Derivation cohort: univariate analysis of patient clinical variables considered potential risk factors for delirium at admission. Mean (SD)

Variables	Delirium	No delirium	p
Age (years)	83.83 (9.8)	74.75 (13.4)	0.000
Blood pressure (mmHg)	127.5 (27.1)	132.3 (26.5)	0.22
Respiratory rate (breaths/min)	27.92 (9.6)	24.42 (6.6)	0.001
Heart rate (beats/min)	86.6 (23.8)	84.06 (22.5)	N.S
Body temperature (°C)	36.7 (0.7)	36.7 (0.8)	N.S
Women (%)	26 (50)	171 (49.6)	NS
Excess alcohol intake (%)	2 (3.8)	19 (5.5)	NS
Mean length of stay in hospital (days)	9.3 (6.6)	8.3 (5.6)	N.S
Admission in previous year (%)	26 (50)	152 (44.1)	NS
Admission in previous month (%)	8(15.1)	45 (84.9)	NS

Table 3 Derivation cohort: univariate analysis of patient blood test results at admission. Mean (SD)

Variables	Delirium	No delirium	p
Haematocrit (%)	39.31 (7.6)	37.42 (6.5)	0.058
Urea (mg/dl)	62.3 (31.6)	60.3 (40.7)	N.S
Creatinine (mg/dl)	1.14 (0.5)	1.25 (0.9)	N.S
Sodium (mEq/l)	138.5 (5.6)	173.9 (5.5)	N.S
Potassium (mEq/l)	5.2 (6.9)	4.8 (0.7)	N.S
Glucose (mg/dl)	140.1 (66.3)	140.8 (78.8)	N.S
White blood cells (10e3/µl)	12.1 (12.2)	10.1(4.7)	N.S
Neutrophils (10e3/µl)	9.8 (8.5)	10.8 (14.8)	N.S

Table 4 Derivation cohort: univariate analysis of patient medication prior to admission.

Variables	Delirium	No delirium	p
Antidepressants	16 (30.8)	59 (17.1)	0.023
Antidementia drugs	5 (9.6)	15 (4.3)	0.16
Antipsychotics	8 (15.4)	16 (4.6)	0.007
Anticonvulsants	5 (9.6)	15 (4.3)	0.16
Benzodiazepines	23 (44.2)	139 (40.3)	NS

Table 5 Derivation cohort: variables characterising patient status on admission

Variables	Delirium	No delirium	p
Urinary catheter	13 (25)	37(10.7)	NS
Fluid therapy	29 (55.8)	124 (35.9)	0.009
Vision impairment	36 (69.2)	192 (55.7)	0.072
Hearing impairment	9 (17.3)	87 (25.2)	NS
Oxygen therapy	32 (61.5)	202 (58.6)	NS
Pressure ulcers	3 (5.8)	25 (7.3)	NS
Level of consciousness	5 (21.7)	18 (78.3)	0.20
Dementia	18 (34.6)	49 (14.2)	0.001
Infection	28 (53.8)	141(40.8)	0.097

Table 6 Derivation cohort: univariate analysis of patient activities of daily living

Variables	Delirium	No delirium	p
Impaired personal hygiene and grooming	39 (75)	116 (33.6)	0.0001
Impaired dressing and undressing	38 (73.1)	117 (33.9)	0.0001
Impaired getting onto or off toilet	36 (69.2)	110 (31.9)	0.001
Impaired ambulation	38 (73.1)	125 (36.2)	0.001
Impaired bowel and bladder control	36 (69.2)	103 (29.9)	0.001
Impaired self-feeding	31 (59.6)	78 (22.6)	0.000
Dependence in ≥ 5 activities	36 (69.2)	87(25.2)	0.0001

Table 7 Variables included in the logistic regression model

Variables	B	SE	Wald	Degrees of freedom	Sig.	Exp(B)
Age [1]	1.381	0.349	15.664	1	0.000	3.978
DADLs[2]	1.397	0.350	15.924	1	0.000	4.042
Drugs[3]	1.515	0.443	11.715	1	0.001	4.547
Constant	-3.234	0.295	120.122	1	0.000	0.039

Hosmer and Lemeshow goodness of fit test p= 0.873

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[1] Age: > 85 years old

[2] DADLs: Dependence in 5 or more activities of daily livings

[3] Drugs: total of 2 or more points for drugs taken on admission where antidepressants, antidementia drugs, and anticonvulsants score 1 point each, and antipsychotics score 2 points

Table 8 Logistic regression model

Group	Points on the prediction rule	Incidence of delirium (%)	OR	AUC (IC 95%)
Derivation cohort (n=397)				0.77 (0.73-0.82)
	0	9/219 (4)	Reference	
	1	16/116 (14)	3.7 (1.5-8.7)	
	≥2	27/62 (43)	18 (7.8-41.5)	
Validation cohort (n=302)				0.85 (0.8-0.88)
	0	5/142 (3.5)	Reference	
	1	18/77 (23)	8.3 (2.9-23.6)	
	≥2	53/83 (64)	48.4 (17.8-131.4)	

Table 9 A 2 X 2 table for the validation cohort

Cut-off point	Delirium	No delirium	Total
0 (negative)	5	137	142
≥1 (positive)	71	89	160
	76	226	302

Sensitivity = 93.4%, 95% CI 85.5 to 97.2

Specificity = 60.6%, 95% CI 54.1 to 66.8

PPV = 44.4%, 95% CI 36.9 to 52.1

NPV = 96.5%, 95% CI 92 to 98.5

Figure 1: ROC curve for the derivation cohort

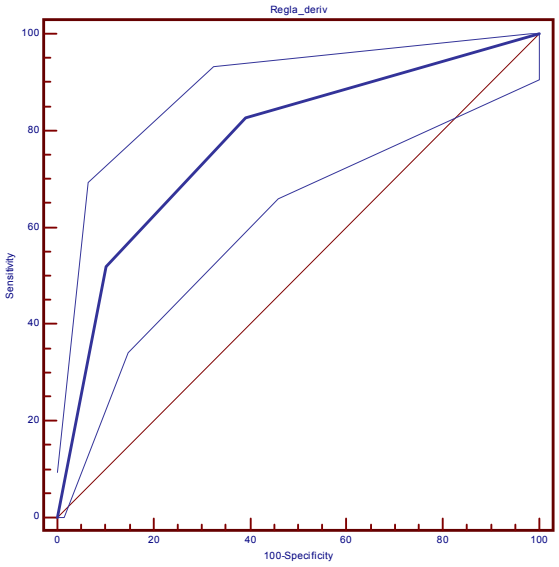
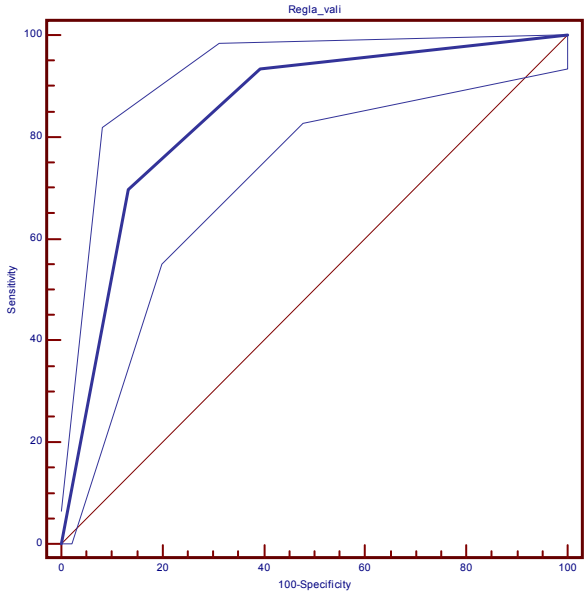


Figure 2: ROC curve for the validation cohort



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DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN OBSERVATIONAL STUDY.

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DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN OBSERVATIONAL STUDY.

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ABSTRACT

Objectives: To develop and validate a simple clinical prediction rule, based on variables easily measurable at admission, to identify patients at high risk of developing delirium during their hospital stay on an internal medicine ward.

Design: Prospective study of two cohorts of patients admitted between May 1st and June 30th 2008 (derivation cohort), and between May 1st and June 30th 2009 (validation cohort).

Setting: A tertiary hospital in Donostia-Gipuzkoa (Spain)

Participants: 397 patients participated in the study. The mean age and incidence of delirium were 75.9 years and 13% respectively in the derivation cohort, and 75.8 years and 25% in the validation cohort.

Main outcome measures: The predictive variables analysed and finally included in the rule were: being aged 85 years old or older, being dependent in 5 or more activities of daily living, and taking 2 or more psychotropic drugs (antipsychotics, benzodiazepines, antidepressants, anticonvulsant, and/or antidementia drugs). The variable of interest was delirium as defined by the short Confusion Assessment Method, which assesses four characteristics: acute onset and fluctuating course, inattention, disorganised thinking, and altered level of consciousness.

Results: We developed a rule in which the individual risk of delirium is obtained by adding 1 point for each criterion met (age≥85, high level of dependence, and being on psychotropic medication). The result is considered positive if the score is ≥ 1. The rule accuracy was: sensitivity = 93.4% (95% CI: 85.5-97.2),

specificity = 60.6% (95% CI: 54.1-66.8), PPV = 44.4% (95% CI: 36.9-52.1), and NPV = 96.5% (95% CI: 92-98.5). The area under the ROC curve was 0.85 for the validation cohort.

Conclusions: The presence or absence of any of the three predictive factors (age≥85, high level of dependence, and psychotropic medication) allowed us to classify patients on internal medicine wards according to the risk of developing delirium. The simplicity of the variables in our clinical prediction rule means that the data collection required is feasible in busy medicine units.

Introduction:

Delirium, also referred to as acute confusional state, is an acute disturbance of attention and cognition with a fluctuating course that often appears in hospitalised patients. Between 10% and 30% of patients admitted to general hospitals develop delirium,[1-3] with a prevalence of up to 60% among frail elderly patients.[4] It is a serious complication that increases mortality[5] and reduces the functional status of patients,[6] as well as increasing the length of hospital stays[7-8] and rates of readmission.[9] While the pathophysiology of delirium remains poorly understood, multiple risk factors have been identified.[10] These can be classified into two groups: factors that increase baseline vulnerability (presence of dementia, cerebrovascular accident, Parkinson´s disease, old age, and sensory impairment, among others);[11] and those that may be a trigger (such as polypharmacy, infection, and dehydration).[12-14]

Various interventions to improve modifiable variables have been found effective in preventing the occurrence of delirium.[15-18] Therefore; the identification of patients at high risk of developing delirium is particularly important.[19]

Clinical prediction rules are useful tools for classifying patients at different levels of risk.[20] Other authors proposed a rule to predict the risk of developing delirium[21] for use in patients admitted due to clinical worsening of their condition, but its use has not become widespread in our setting since it requires variables that are difficult to measure on admission (Mini-Mental State Examination score, and visual acuity, among others).

The objective of this study was to derive and validate a simple clinical prediction rule, based on variables that are easily measurable and are often routinely taken on admission, to identify patients at high risk of developing delirium during their hospital stay on an internal medicine ward.

The identification of these patients will allow us to introduce the necessary preventative measures.

Methods

Design

To develop the clinical prediction rule we assessed a prospective cohort of consecutive patients admitted in four internal medicine wards. Subsequently, we assessed a different prospective cohort of consecutive patients to validate the rule.

Patients

The derivation cohort was 397 consecutive patients aged 18 years or over, of both sexes, who were admitted to any of four internal medicine wards at Donostia Hospital between May 1st 2008 and June 30th 2008, and we used no other exclusion criteria. The following year, between May 1st 2009 and June 30th 2009, we recruited the validation cohort on the same basis: 302 consecutive patients aged 18 or over, of both sexes, who were admitted to any of the same four internal medicine wards at the hospital. The consent was obtained from the study participants and all patients gave their consent to participate in the study.

Assessment of delirium

We defined delirium using the short version of the Confusion Assessment Method,[22] a short form for assessing confusion. This diagnostic algorithm assesses four characteristics: 1) acute onset and fluctuating course, 2)

inattention, 3) disorganised thinking, and 4) altered level of consciousness. The diagnosis of delirium required the presence of 1) and 2), and either 3) or 4) (or both). This assessment was performed by two independent researchers, when it was considered that patients were ready for discharge, after analysis of any relevant data in their medical record and nursing report. Disagreements were resolved by consensus with a third researcher. All these evaluators were blinded to the potential predictive variables selected for the study.

Potential predictors

The potential predictive variables for delirium were selected after a systematic review of the literature[10-14 23-25]. We sought to identify variables that were easy to measure and are often routinely recorded on admission to these wards.

The following variables were selected and measured on admission: age (years), sex, systolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/minute), axillary temperature (℃), oxygen therapy (no: not used; and yes: oxygen with nasal cannula, mask, and/or oxygen at home), fluid therapy, presence of urinary catheter, level of consciousness (normal: alert; or altered: drowsiness, unresponsiveness to voice, unresponsiveness to pain, and/or generally unresponsive), diagnosis of infection at admission (respiratory, urinary or other types of infections; or no infection: any other cause of admission), admission in the previous year, admission in the previous month, hearing impairment (use of a hearing aid, or deafness reported by the patient or caregiver), vision impairment (regular use of glasses or reduction in visual acuity reported by the patient or caregiver), and dementia (in a medical report or

reported by the caregiver). In addition, blood tests were taken on admission to measure the following: haematocrit (%), levels of urea (mg/dl), creatinine (mg/dl), sodium (mEq/l), potassium (mEq/l), and glucose (mg/dl), as well as white blood cell (10e3/µl) and neutrophil (10e3/µl) counts. Lastly, certain characteristics of patients prior to admission were also assessed: level of dependence for activities of daily living (personal hygiene and grooming, dressing and undressing, getting onto or off toilet, ambulation, bowel and bladder control, and self-feeding) as dichotomous variables (dependent; independent); presence of pressure ulcers, and excess alcohol intake (>60 g/ethanol/day), as well as use of certain types of medication: benzodiazepines, antidepressants, antidementia drugs, antipsychotics, anti-Parkinson's drugs, or anticonvulsants.

Statistical analysis

A descriptive analysis was carried out, based on the calculation of means and standard deviations for continuous variables, and absolute or relative frequencies as percentages for categorical variables. Subsequently, some continuous variables were dichotomised using the median value.

Sample size

Assuming a prevalence of delirium at admission of 10%, it was calculated that we needed 10 patients with delirium for each variable included in the model, with the intention that the model should be as parsimonious as possible.

Comparison between derivation and validation cohorts

We compared the characteristics of patients in the derivation cohort with those in the validation cohort using the Student's t-test for continuous variables and the Chi square test for ordinal and dichotomous variables.

Derivation of the prediction rule

The characteristics of patients who developed delirium were compared with those of patients who did not, again using the Student's t-test or the Chi square test as appropriate. A p-value <0.25 was taken to indicate potentially predictive variables and those meeting this criteria were included in the multivariate model. Then, using a stepwise logistic regression model we selected the terms (predictive variables) to be included in the final model. The criteria for entry in the model and for removal were $p \leq 0.05$ and $p \geq 0.10$ respectively. The Hosmer Lemeshow test was performed to assess the goodness of fit of this model.

We note that we also explored selecting variables for an alternative prediction rule by recursive partitioning. However, as the performance of this rule was poorer than that of the rule obtained by logistic regression, we decided to report exclusively the data concerning the rule derived using the latter method.

Validation cohort and model performance

The clinical prediction rule was applied to the validation cohort. We report the incidence of delirium as a function of score on the rule and the ORs using the

lowest risk category as the reference. The performance of the rule in the two cohorts was explored using ROC curve analysis.

To assess the predictive accuracy of the rule, we constructed a 2x2 table for calculation of the following: sensitivity, specificity, and positive and negative predictive values. The 95% confidence intervals of these indicators were also calculated assuming a binomial distribution.

We used SPSS 19.0 and MedCalc for all the analysis.

Results

In the validation cohort, 13% of patients (52 out of 397) developed delirium, and in the derivation cohort the incidence was 25.2% (76 out 302). Table 1 summarises baseline characteristics of the derivation and validation cohorts. Patients included in our study were elderly (76.4±13.3 years old) and slightly more than half were women (52%, 362 out of 699). The derivation and validation cohorts were similar in some respects, namely, age, sex, mean length of stay, and types of medication. On the other hand, patients in the validation cohort were significantly more dependant in certain activities of daily living: personal hygiene and grooming, dressing and undressing, and getting onto or off toilet.

Tables 2 to 6 report the results of the univariate analysis in which the risk factors were compared between patients who developed delirium and those who did not within the derivation cohort. Those who developed delirium were significantly older and had slightly higher respiratory rates, but there were no significant differences in blood test results.

Age was dichotomised using a cut-off of 85 years, a value that was found to have a sensitivity of 85% and a specificity of 56% for delirium by the ROC curve analysis. We found that the risk of delirium associated with the types of medication considered was similar for all except antipsychotic drugs, for which the risk was twice as high. Accordingly, the medication data was coded according to the number of different drugs patients were taking at admission with each antidepressant, antidementia, or anticonvulsant drug contributing equally, while antipsychotic drugs were weighted by a factor of two. The

activities of daily living data were also dichotomised with a cut-off of reported impairments in five activities.

The scores for the clinical prediction rule were assigned on the basis of regression coefficients obtained in the logistic regression model (Table 7). One point was given to patients older than 85 years, to those who had 2 or more points in the variable drugs, and to those with impairments in five or more of the activities of daily living considered. Therefore, the total score for the rule ranged between 0 and 3.

The patients with delirium of the two cohorts scored similarly: 17% and 7% scored 0, 48% and 30% scored ≤ 1 and 85% and 85% scored ≤ 2 in the derivation and validation cohort respectively.

Table 9 and Figures 1 and 2 describe the performance of the rule in the derivation and validation cohorts. In both cohorts, we observed higher rates of delirium associated with higher scores on the rule, the model having a good predictive power for the validation cohort (area under the ROC curve, AUC = 0.85). In contrast with what would be expected, the values obtained in the validation cohort are better than those obtained in the derivation cohort, and this is probably related to the higher incidence of delirium in validation group.

In particular, Table 9 lists the sensitivity (Se) and specificity (Sp), as well as the positive and negative predictive values (PPVs and NPVs) obtained when the rule was dichotomised as negative (a score of 0) or positive (as score of ≥1). For the validation cohort, the Se, Sp, NPV, and PPV were 93.4%, 60.6%, 96%, and 44% respectively

DISCUSSION

In this prospective study, we identified three independent predictive factors for delirium: being 85 years old or older, being dependent in five or more activities of daily living (of the six considered), and taking psychotropic drugs (antipsychotics, benzodiazepines, antidepressants, anticonvulsants, and/or antidementia drugs). With these factors we developed a clinical prediction rule in which an individual risk score for delirium is obtained by adding 1 point for each of the factors present. Applying this rule, patients are classified as positive if they have a total score of 1 or more.

In the derivation cohort, 13% of patients developed delirium, while the incidence was somewhat higher, 25%, in the validation cohort. Patients were elderly (mean ages in the derivation and validation cohorts were 75.9 +/- 13.3 years and 76.8 +/- 13.3 years respectively), and there were slightly more women (52%). The mean length of hospital stay was 8 +/- 5.8 days and overall mortality was 5%. There is a significant difference in the ADL variables being those from the validation cohort more dependent than the derivation cohort. All the above mention variables explain the almost two fold discrepancy in the incidence of delirium between the two cohort.

There are multiple factors for the development of delirium, the predisposing and triggering factors being well defined. The predisposing factors are mostly related to degenerative brain disease (dementia, arteriosclerosis, Parkinson´s disease, and depression).[10 11] On the other hand, there are a diverse range of triggering factors, in particular, medication, the presence of infection, surgery, metabolic disorders, and water-electrolyte imbalances, among others.[13 14 23-25]

In the present study, we have only explored variables that are readily available on admission, in order to use the predictive rule at that stage and be able to introduce preventative measures immediately in high-risk patients. These would include trying to avoid triggering factors for the development of delirium (such as changes of room/ward, unnecessary catheterisation, inadequate oral hydration, and polypharmacy).

Interestingly, the factors found to be good predictors for the development of delirium in our study (age≥85, high level of dependence, and being on psychotropic medication), to some extent, indirectly reflect the severity of the organic brain damage in patients with delirium.

Another predictive rule for delirium in this type of patients has been published[21] but showed a significantly lower performance than that we obtained (AUC = 0.66 [0.55-077] vs. AUC=0.85 [0.80-0.90] with our rule). Further, in our opinion, it is also more difficult to apply than the rule we propose. The simplicity of the variables included in our rule makes data collection a feasible task for busy healthcare units.

Between 10% and 60% of patients admitted to hospital develop delirium, depending on the type of patient, the incidence in frail elderly patients being at the top of this range. In our study, it was 13% and 25% in the derivation and validations cohorts, respectively. Delirium is well known to be difficult to diagnose and a wide range of instruments have been developed to help detect the condition.[26 27] We used the Confusion Assessment Method[22] that has a sensitivity of 96% (95% CI 80-100%) and a specificity of 93% (95% CI 84-100%). In our study, the doctors in charge of the diagnosis of delirium were

specialists in internal medicine, with considerable training and experience in the management of this type of patients, any differences being resolved by consensus with a third specialist. We note, however, that the diagnoses of delirium were not confirmed by a psychiatrist. This may partially explain the low incidence of delirium in our patients, that is, it may be that only the most clinically striking cases, those which required pharmacological treatment, were recognised.

The association between delirium and an increase of morbidity and mortality[5 6 9] is well known, as are the effectiveness of preventive measures to avoid the development of the disease.[15-18] The use of the proposed predictive rule would allow us to classify around half of our inpatients (53%) as high-risk. Taking preventative measures in this high risk group, up to 93.4% of those who developed delirium in our study would have been covered by the measures and might not have then developed the condition.

It would be interesting for the clinical predictive rule we propose to be validated in other cohorts of frail elderly patients with worsening of multiple medical conditions to check its external validity.

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Table 1 Characteristics of patients in the derivation and validation cohorts

Characteristics	Derivation cohort (n=397)	Validation cohort (n= 302)	p
Mean age (SD)	75.9 (13.3)	76.8 (13.3)	N.S
Mean length of stay (SD)	8.4 (5.8)	8 (6.1)	N.S
Women (%)	197 (49.6)	165 (54.3)	N.S
Medication (%)			
Benzodiazepines	162 (40.8)	134 (44.4)	N.S
Antidepressants	75 (18.9)	74 (24.5)	N.S
Antidementia drugs	20 (5)	11 (3.6)	N.S
antipsychotics	24 (6)	21 (7)	N.S
Anti-Parkinson´s agents	13 (3.3)	6(2)	N.S
Anticonvulsants	20 (5)	16 (5.3)	N.S
Dependence in activities of daily living (%)			
Personal hygiene and grooming	155 (39)	171 (56.6)	<0.05
Dressing and undressing	155 (39)	174 (57.6)	<0.05
Getting onto or off toilet	146 (36.8)	161 (53.3)	<0.05
Ambulation	163 (41.1)	166 (55)	<0.05
Bowel and bladder control	139 (35)	122 (40.4)	N.S
Self-feeding	109 (27.5)	102 (33.8)	N.S

Table 2 Derivation cohort: univariate analysis of patient clinical variables considered potential risk factors for delirium at admission. Mean (SD)

Variables	Delirium	No delirium	p
Age (years)	83.83 (9.8)	74.75 (13.4)	0.000
Blood pressure (mmHg)	127.5 (27.1)	132.3 (26.5)	0.22
Respiratory rate (breaths/min)	27.92 (9.6)	24.42 (6.6)	0.001
Heart rate (beats/min)	86.6 (23.8)	84.06 (22.5)	N.S
Body temperature (°C)	36.7 (0.7)	36.7 (0.8)	N.S
Women (%)	26 (50)	171 (49.6)	NS
Excess alcohol intake (%)	2 (3.8)	19 (5.5)	NS
Mean length of stay in hospital (days)	9.3 (6.6)	8.3 (5.6)	N.S
Admission in previous year (%)	26 (50)	152 (44.1)	NS
Admission in previous month (%)	8(15.1)	45 (84.9)	NS

Table 3 Derivation cohort: univariate analysis of patient blood test results at admission. Mean (SD)

Variables	Delirium	No delirium	p
Haematocrit (%)	39.31 (7.6)	37.42 (6.5)	0.058
Urea (mg/dl)	62.3 (31.6)	60.3 (40.7)	N.S
Creatinine (mg/dl)	1.14 (0.5)	1.25 (0.9)	N.S
Sodium (mEq/l)	138.5 (5.6)	173.9 (5.5)	N.S
Potassium (mEq/l)	5.2 (6.9)	4.8 (0.7)	N.S
Glucose (mg/dl)	140.1 (66.3)	140.8 (78.8)	N.S
White blood cells (10e3/µl)	12.1 (12.2)	10.1(4.7)	N.S
Neutrophils (10e3/µl)	9.8 (8.5)	10.8 (14.8)	N.S

Table 4 Derivation cohort: univariate analysis of patient medication prior to admission.

Variables	Delirium	No delirium	p
Antidepressants	16 (30.8)	59 (17.1)	0.023
Antidementia drugs	5 (9.6)	15 (4.3)	0.16
Antipsychotics	8 (15.4)	16 (4.6)	0.007
Anticonvulsants	5 (9.6)	15 (4.3)	0.16
Benzodiazepines	23 (44.2)	139 (40.3)	NS

Table 5 Derivation cohort: variables characterising patient status on admission

Variables	Delirium	No delirium	p
Urinary catheter	13 (25)	37(10.7)	NS
Fluid therapy	29 (55.8)	124 (35.9)	0.009
Vision impairment	36 (69.2)	192 (55.7)	0.072
Hearing impairment	9 (17.3)	87 (25.2)	NS
Oxygen therapy	32 (61.5)	202 (58.6)	NS
Pressure ulcers	3 (5.8)	25 (7.3)	NS
Level of consciousness	5 (21.7)	18 (78.3)	0.20
Dementia	18 (34.6)	49 (14.2)	0.001
Infection	28 (53.8)	141(40.8)	0.097

Table 6 Derivation cohort: univariate analysis of patient activities of daily living

Variables	Delirium	No delirium	p
Impaired personal hygiene and grooming	39 (75)	116 (33.6)	0.0001
Impaired dressing and undressing	38 (73.1)	117 (33.9)	0.0001
Impaired getting onto or off toilet	36 (69.2)	110 (31.9)	0.001
Impaired ambulation	38 (73.1)	125 (36.2)	0.001
Impaired bowel and bladder control	36 (69.2)	103 (29.9)	0.001
Impaired self-feeding	31 (59.6)	78 (22.6)	0.000
Dependence in ≥ 5 activities	36 (69.2)	87(25.2)	0.0001

Table 7 Variables included in the logistic regression model

Variables	B	SE	Wald	Degrees of freedom	Sig.	Exp(B)
Age [1]	1.381	0.349	15.664	1	0.000	3.978
DADLs[2]	1.397	0.350	15.924	1	0.000	4.042
Drugs[3]	1.515	0.443	11.715	1	0.001	4.547
Constant	-3.234	0.295	120.122	1	0.000	0.039

Hosmer and Lemeshow goodness of fit test p= 0.873

[1] Age: > 85 years old

[2] DADLs: Dependence in 5 or more activities of daily livings

[3] Drugs: total of 2 or more points for drugs taken on admission where antidepressants, antidementia drugs, and anticonvulsants score 1 point each, and antipsychotics score 2 points

Table 8 Logistic regression model

Group	Points on the prediction rule	Incidence of delirium (%)	OR	AUC (IC 95%)
Derivation cohort (n=397)				0.77 (0.73-0.82)
	0	9/219 (4)	Reference	
	1	16/116 (14)	3.7 (1.5-8.7)	
	≥2	27/62 (43)	18 (7.8-41.5)	
Validation cohort (n=302)				0.85 (0.8-0.88)
	0	5/142 (3.5)	Reference	
	1	18/77 (23)	8.3 (2.9-23.6)	
	≥2	53/83 (64)	48.4 (17.8-131.4)	

Table 9 A 2 X 2 table for the validation cohort

Cut-off point	Delirium	No delirium	Total
0 (negative)	5	137	142
≥1 (positive)	71	89	160
	76	226	302

Sensitivity = 93.4%, 95% CI 85.5 to 97.2

Specificity = 60.6%, 95% CI 54.1 to 66.8

PPV = 44.4%, 95% CI 36.9 to 52.1

NPV = 96.5%, 95% CI 92 to 98.5

DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN OBSERVATIONAL STUDY.

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ABSTRACT

Objectives: To develop and validate a simple clinical prediction rule, based on variables easily measurable at admission, to identify patients at high risk of developing delirium during their hospital stay on an internal medicine ward.

Design: Prospective study of two cohorts of patients admitted between May 1st and June 30th 2008 (derivation cohort), and between May 1st and June 30th 2009 (validation cohort).

Setting: A tertiary hospital in Donostia-Gipuzkoa (Spain)

Participants: 397 patients participated in the study. The mean age and incid~~preval~~ence of delirium were 75.9 years and 13% respectively in the derivation cohort, and 75.8 years and 25% in the validation cohort.

Main outcome measures: The predictive variables analysed and finally included in the rule were: being aged 85 years old or older, being dependent in 5 or more activities of daily living, and taking 2 or more psychotropic drugs (antipsychotics, benzodiazepines, antidepressants, anticonvulsant, and/or antidementia drugs). The variable of interest was delirium as defined by the short Confusion Assessment Method, which assesses four characteristics: acute onset and fluctuating course, inattention, disorganised thinking, and altered level of consciousness.

Results: We developed a rule in which the individual risk of delirium is obtained by adding 1 point for each criterion met (age≥85, high level of dependence, and being on psychotropic medication). The result is considered positive if the score is ≥ 1. The rule accuracy was: sensitivity = 93.4% (95% CI: 85.5-97.2),

specificity = 60.6% (95% CI: 54.1-66.8), PPV = 44.4% (95% CI: 36.9-52.1), and NPV = 96.5% (95% CI: 92-98.5). The area under the ROC curve was 0.85 for the validation cohort.

Conclusions: The presence or absence of any of the three predictive factors (age≥85, high level of dependence, and psychotropic medication) allowed us to classify patients on internal medicine wards according to the risk of developing delirium. The simplicity of the variables in our clinical prediction rule means that the data collection required is feasible in busy medicine units.

Introduction:

Delirium, also referred to as acute confusional state, is an acute disturbance of attention and cognition with a fluctuating course that often appears in hospitalised patients. Between 10% and 30% of patients admitted to general hospitals develop delirium,[1-3] with a prevalence of up to 60% among frail elderly patients.[4] It is a serious complication that increases mortality[5] and reduces the functional status of patients,[6] as well as increasing the length of hospital stays[7-8] and rates of readmission.[9] While the pathophysiology of delirium remains poorly understood, multiple risk factors have been identified.[10] These can be classified into two groups: factors that increase baseline vulnerability (presence of dementia, cerebrovascular accident, Parkinson´s disease, old age, and sensory impairment, among others);[11] and those that may be a trigger (such as polypharmacy, infection, and dehydration).[12-14]

Various interventions to improve modifiable variables have been found effective in preventing the occurrence of delirium.[15-18] Therefore; the identification of patients at high risk of developing delirium is particularly important.[19]

Clinical prediction rules are useful tools for classifying patients at different levels of risk.[20] Other authors proposed a rule to predict the risk of developing delirium[21] for use in patients admitted due to clinical worsening of their condition, but its use has not become widespread in our setting since it requires variables that are difficult to measure on admission (Mini-Mental State Examination score, and visual acuity, among others).

The objective of this study was to derive and validate a simple clinical prediction rule, based on variables that are easily measurable and are often routinely taken on admission, to identify patients at high risk of developing delirium during their hospital stay on an internal medicine ward.

The identification of these patients will allow us to introduce the necessary preventative measures.

Methods

Design

To develop the clinical prediction rule we assessed a prospective cohort of consecutive patients admitted in four internal medicine wards. Subsequently, we assessed a different prospective cohort of consecutive patients to validate the rule.

Patients

The derivation cohort was 397 consecutive patients aged 18 years or over, of both sexes, who were admitted to any of four internal medicine wards at Donostia Hospital between May 1st 2008 and June 30th 2008, and we used no other exclusion criteria. The following year, between May 1st 2009 and June 30th 2009, we recruited the validation cohort on the same basis: 302 consecutive patients aged 18 or over, of both sexes, who were admitted to any of the same four internal medicine wards at the hospital. The consent was obtained from the study participants and all patients gave their consent to participate in the study.

Assessment of delirium

We defined delirium using the short version of the Confusion Assessment Method,[22] a short form for assessing confusion. This diagnostic algorithm assesses four characteristics: 1) acute onset and fluctuating course, 2)

inattention, 3) disorganised thinking, and 4) altered level of consciousness. The diagnosis of delirium required the presence of 1) and 2), and either 3) or 4) (or both). This assessment was performed by two independent researchers, when it was considered that patients were ready for discharge, after analysis of any relevant data in their medical record and nursing report. Disagreements were resolved by consensus with a third researcher. All these evaluators were blinded to the potential predictive variables selected for the study.

Potential predictors

The potential predictive variables for delirium were selected after a systematic review of the literature[10-14 23-25]. We sought to identify variables that were easy to measure and are often routinely recorded on admission to these wards.

The following variables were selected and measured on admission: age (years), sex, systolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/minute), axillary temperature (°C), oxygen therapy (no: not used; and yes: oxygen with nasal cannula, mask, and/or oxygen at home), fluid therapy, presence of urinary catheter, level of consciousness (normal: alert; or altered: drowsiness, unresponsiveness to voice, unresponsiveness to pain, and/or generally unresponsive), diagnosis of infection at admission (respiratory, urinary or other types of infections; or no infection: any other cause of admission), admission in the previous year, admission in the previous month, hearing impairment (use of a hearing aid, or deafness reported by the patient or caregiver), vision impairment (regular use of glasses or reduction in visual acuity reported by the patient or caregiver), and dementia (in a medical report or

reported by the caregiver). In addition, blood tests were taken on admission to measure the following: haematocrit (%), levels of urea (mg/dl), creatinine (mg/dl), sodium (mEq/l), potassium (mEq/l), and glucose (mg/dl), as well as white blood cell (10e3/µl) and neutrophil (10e3/µl) counts. Lastly, certain characteristics of patients prior to admission were also assessed: level of dependence for activities of daily living (personal hygiene and grooming, dressing and undressing, getting onto or off toilet, ambulation, bowel and bladder control, and self-feeding) as dichotomous variables (dependent; independent); presence of pressure ulcers, and excess alcohol intake (>60 g/ethanol/day), as well as use of certain types of medication: benzodiazepines, antidepressants, antidementia drugs, antipsychotics, anti-Parkinson's drugs, or anticonvulsants.

Statistical analysis

A descriptive analysis was carried out, based on the calculation of means and standard deviations for continuous variables, and absolute or relative frequencies as percentages for categorical variables. Subsequently, some continuous variables were dichotomised using the median value.

Sample size

Assuming a prevalence of delirium at admission of 10%, it was calculated that we needed 10 patients with delirium for each variable included in the model, with the intention that the model should be as parsimonious as possible.

Comparison between derivation and validation cohorts

We compared the characteristics of patients in the derivation cohort with those in the validation cohort using the Student's t-test for continuous variables and the Chi square test for ordinal and dichotomous variables.

Derivation of the prediction rule

The characteristics of patients who developed delirium were compared with those of patients who did not, again using the Student's t-test or the Chi square test as appropriate. A p-value <0.25 was taken to indicate potentially predictive variables and those meeting this criteria were included in the multivariate model. Then, using a stepwise logistic regression model we selected the terms (predictive variables) to be included in the final model. The criteria for entry in the model and for removal were $p \leq 0.05$ and $p \geq 0.10$ respectively. The Hosmer Lemeshow test was performed to assess the goodness of fit of this model.

We note that we also explored selecting variables for an alternative prediction rule by recursive partitioning. However, as the performance of this rule was poorer than that of the rule obtained by logistic regression, we decided to report exclusively the data concerning the rule derived using the latter method.

Validation cohort and model performance

The clinical prediction rule was applied to the validation cohort. We report the incidence of delirium as a function of score on the rule and the ORs using the

lowest risk category as the reference. The performance of the rule in the two cohorts was explored using ROC curve analysis.

To assess the predictive~~diagnostic~~ accuracy of the rule, we constructed a 2x2 table for calculation of the following: sensitivity, specificity, and positive and negative predictive values. The 95% confidence intervals of these indicators were also calculated assuming a binomial distribution.

We used SPSS 19.0 and MedCalc for all the analysis.

Results

In the validation cohort, 13% of patients (52 out of 397) developed delirium, and in the derivation cohort the incidprevalence was 25.2% (76 out 302). Table 1 summarises baseline characteristics of the derivation and validation cohorts. Patients included in our study were elderly (76.4±13.3 years old) and slightly more than half were women (52%, 362 out of 699). The derivation and validation cohorts were similar in some respects, namely, age, sex, mean length of stay, and types of medication. On the other hand, patients in the validation cohort were significantly more dependant in certain activities of daily living: personal hygiene and grooming, dressing and undressing, and getting onto or off toilet.

Tables 2 to 6 report the results of the univariate analysis in which the risk factors were compared between patients who developed delirium and those who did not within the derivation cohort. Those who developed delirium were significantly older and had slightly higher respiratory rates, but there were no significant differences in blood test results.

Age was dichotomised using a cut-off of 85 years, a value that was found to have a sensitivity of 85% and a specificity of 56% for delirium by the ROC curve analysis. We found that the risk of delirium associated with the types of medication considered was similar for all except antipsychotic drugs, for which the risk was twice as high. Accordingly, the medication data was coded according to the number of different drugs patients were taking at admission with each antidepressant, antidementia, or anticonvulsant drug contributing equally, while antipsychotic drugs were weighted by a factor of two. The

activities of daily living data were also dichotomised with a cut-off of reported impairments in five activities.

The scores for the clinical prediction rule were assigned on the basis of regression coefficients obtained in the logistic regression model (Table 7). One point was given to patients older than 85 years, to those who had 2 or more points in the variable drugs, and to those with impairments in five or more of the activities of daily living considered. Therefore, the total score for the rule ranged between 0 and 3.

The patients with delirium of the two cohorts scored similarly: 17% and 7% scored 0, 48% and 30% scored ≤ 1 and 85% and 85% scored ≤ 2 in the derivation and validation cohort respectively.

Table 9 and Figures 1 and 2 describe the performance of the rule in the derivation and validation cohorts. In both cohorts, we observed higher rates of delirium associated with higher scores on the rule, the model having a good predictive power for the validation cohort (area under the ROC curve, AUC = 0.85). In contrast with what would be expected, the values obtained in the validation cohort are better than those obtained in the derivation cohort, and this is probably related to the higher incid~~preval~~ence of delirium in validation group.

In particular, Table 9 lists the sensitivity (Se) and specificity (Sp), as well as the positive and negative predictive values (PPVs and NPVs) obtained when the rule was dichotomised as negative (a score of 0) or positive (as score of ≥1). For the validation cohort, the Se, Sp, NPV, and PPV were 93.4%, 60.6%, 96%, and 44% respectively

DISCUSSION

In this prospective study, we identified three independent predictive factors for delirium: being 85 years old or older, being dependent in five or more activities of daily living (of the six considered), and taking psychotropic drugs (antipsychotics, benzodiazepines, antidepressants, anticonvulsants, and/or antidementia drugs). With these factors we developed a clinical prediction rule in which an individual risk score for delirium is obtained by adding 1 point for each of the factors present. Applying this rule, patients are classified as positive if they have a total score of 1 or more.

In the derivation cohort, 13% of patients developed delirium, while the incid~~preval~~ence was somewhat higher, 25%, in the validation cohort. Patients were elderly (mean ages in the derivation and validation cohorts were 75.9 +/- 13.3 years and 76.8 +/- 13.3 years respectively), and there were slightly more women (52%). The mean length of hospital stay was 8 +/- 5.8 days and overall mortality was 5%. There is a significant difference in the ADL variables being those from the validation cohort more dependent than the derivation cohort. All the above mention variables explain the almost two fold discrepancy in the incidence of delirium between the two cohort.

There are multiple factors for the development of delirium, the predisposing and triggering factors being well defined. The predisposing factors are mostly related to degenerative brain disease (dementia, arteriosclerosis, Parkinson´s disease, and depression).[10 11] On the other hand, there are a diverse range of triggering factors, in particular, medication, the presence of infection, surgery, metabolic disorders, and water-electrolyte imbalances, among others.[13 14 23-25]

In the present study, we have only explored variables that are readily available on admission, in order to use the predictive rule at that stage and be able to introduce preventative measures immediately in high-risk patients. These would include trying to avoid triggering factors for the development of delirium (such as changes of room/ward, unnecessary catheterisation, inadequate oral hydration, and polypharmacy).

Interestingly, the factors found to be good predictors for the development of delirium in our study (age≥85, high level of dependence, and being on psychotropic medication), to some extent, indirectly reflect the severity of the organic brain damage in patients with delirium.

Another predictive rule for delirium in this type of patients has been published[21] but showed a significantly lower performance than that we obtained (AUC = 0.66 [0.55-077] vs. AUC=0.85 [0.80-0.90] with our rule). Further, in our opinion, it is also more difficult to apply than the rule we propose. The simplicity of the variables included in our rule makes data collection a feasible task for busy healthcare units.

Between 10% and 60% of patients admitted to hospital develop delirium, depending on the type of patient, the incid~~preval~~ence in frail elderly patients being at the top of this range. In our study, it was 13% and 25% in the derivation and validations cohorts, respectively. Delirium is well known to be difficult to diagnose and a wide range of instruments have been developed to help detect the condition.[26 27] We used the Confusion Assessment Method[22] that has a sensitivity of 96% (95% CI 80-100%) and a specificity of 93% (95% CI 84-100%). In our study, the doctors in charge of the diagnosis of delirium were

specialists in internal medicine, with considerable training and experience in the management of this type of patients, any differences being resolved by consensus with a third specialist. We note, however, that the diagnoses of delirium were not confirmed by a psychiatrist. This may partially explain the low incid~~preval~~ence of delirium in our patients, that is, it may be that only the most clinically striking cases, those which required pharmacological treatment, were recognised.

The association between delirium and an increase of morbidity and mortality[5 6 9] is well known, as are the effectiveness of preventive measures to avoid the development of the disease.[15-18] The use of the proposed predictive rule would allow us to classify around half of our inpatients (53%) as high-risk. Taking preventative measures in this high risk group, up to 93.4% of those who developed delirium in our study would have been covered by the measures and might not have then developed the condition.

It would be interesting for the clinical predictive rule we propose to be validated in other cohorts of frail elderly patients with worsening of multiple medical conditions to check its external validity.

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CONTRIBUTORS: JM, AB, JIE and IU participated in the design of the study. JM, AB, IB, XG, CA and NL collected all data. JIE and IU carried out the statistical analysis. JM, IU and JIE drafted the manuscript. All authors approved the final version to be published. IU and JM are the guarantors.

COMPETING INTERESTS: All authors have completed the Unified Competing interests form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL: The design was evaluated and then approved by the Clinical Research Ethics Committee of the Gipuzkoa Health region.

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Table 1 Characteristics of patients in the derivation and validation cohorts

Characteristics	Derivation cohort (n=397)	Validation cohort (n= 302)	p
Mean age (SD)	75.9 (13.3)	76.8 (13.3)	N.S
Mean length of stay (SD)	8.4 (5.8)	8 (6.1)	N.S
Women (%)	197 (49.6)	165 (54.3)	N.S
Medication (%)			
Benzodiazepines	162 (40.8)	134 (44.4)	N.S
Antidepressants	75 (18.9)	74 (24.5)	N.S
Antidementia drugs	20 (5)	11 (3.6)	N.S
antipsychotics	24 (6)	21 (7)	N.S
Anti-Parkinson´s agents	13 (3.3)	6(2)	N.S
Anticonvulsants	20 (5)	16 (5.3)	N.S
Dependence in activities of daily living (%)			
Personal hygiene and grooming	155 (39)	171 (56.6)	<0.05
Dressing and undressing	155 (39)	174 (57.6)	<0.05
Getting onto or off toilet	146 (36.8)	161 (53.3)	<0.05
Ambulation	163 (41.1)	166 (55)	<0.05
Bowel and bladder control	139 (35)	122 (40.4)	N.S
Self-feeding	109 (27.5)	102 (33.8)	N.S

Table 2 Derivation cohort: univariate analysis of patient clinical variables considered potential risk factors for delirium at admission. Mean (SD)

Variables	Delirium	No delirium	p
Age (years)	83.83 (9.8)	74.75 (13.4)	0.000
Blood pressure (mmHg)	127.5 (27.1)	132.3 (26.5)	0.22
Respiratory rate (breaths/min)	27.92 (9.6)	24.42 (6.6)	0.001
Heart rate (beats/min)	86.6 (23.8)	84.06 (22.5)	N.S
Body temperature (°C)	36.7 (0.7)	36.7 (0.8)	N.S
Women (%)	26 (50)	171 (49.6)	NS
Excess alcohol intake (%)	2 (3.8)	19 (5.5)	NS
Mean length of stay in hospital (days)	9.3 (6.6)	8.3 (5.6)	N.S
Admission in previous year (%)	26 (50)	152 (44.1)	NS
Admission in previous month (%)	8(15.1)	45 (84.9)	NS

Table 3 Derivation cohort: univariate analysis of patient blood test results at admission. Mean (SD)

Variables	Delirium	No delirium	p
Haematocrit (%)	39.31 (7.6)	37.42 (6.5)	0.058
Urea (mg/dl)	62.3 (31.6)	60.3 (40.7)	N.S
Creatinine (mg/dl)	1.14 (0.5)	1.25 (0.9)	N.S
Sodium (mEq/l)	138.5 (5.6)	173.9 (5.5)	N.S
Potassium (mEq/l)	5.2 (6.9)	4.8 (0.7)	N.S
Glucose (mg/dl)	140.1 (66.3)	140.8 (78.8)	N.S
White blood cells (10e3/µl)	12.1 (12.2)	10.1(4.7)	N.S
Neutrophils (10e3/µl)	9.8 (8.5)	10.8 (14.8)	N.S

Table 4 Derivation cohort: univariate analysis of patient medication prior to admission.

Variables	Delirium	No delirium	p
Antidepressants	16 (30.8)	59 (17.1)	0.023
Antidementia drugs	5 (9.6)	15 (4.3)	0.16
Antipsychotics	8 (15.4)	16 (4.6)	0.007
Anticonvulsants	5 (9.6)	15 (4.3)	0.16
Benzodiazepines	23 (44.2)	139 (40.3)	NS

Table 5 Derivation cohort: variables characterising patient status on admission

Variables	Delirium	No delirium	p
Urinary catheter	13 (25)	37(10.7)	NS
Fluid therapy	29 (55.8)	124 (35.9)	0.009
Vision impairment	36 (69.2)	192 (55.7)	0.072
Hearing impairment	9 (17.3)	87 (25.2)	NS
Oxygen therapy	32 (61.5)	202 (58.6)	NS
Pressure ulcers	3 (5.8)	25 (7.3)	NS
Level of consciousness	5 (21.7)	18 (78.3)	0.20
Dementia	18 (34.6)	49 (14.2)	0.001
Infection	28 (53.8)	141(40.8)	0.097

Table 6 Derivation cohort: univariate analysis of patient activities of daily living

Variables	Delirium	No delirium	p
Impaired personal hygiene and grooming	39 (75)	116 (33.6)	0.0001
Impaired dressing and undressing	38 (73.1)	117 (33.9)	0.0001
Impaired getting onto or off toilet	36 (69.2)	110 (31.9)	0.001
Impaired ambulation	38 (73.1)	125 (36.2)	0.001
Impaired bowel and bladder control	36 (69.2)	103 (29.9)	0.001
Impaired self-feeding	31 (59.6)	78 (22.6)	0.000
Dependence in ≥ 5 activities	36 (69.2)	87(25.2)	0.0001

Table 7 Variables included in the logistic regression model

Variables	B	SE	Wald	Degrees of freedom	Sig.	Exp(B)
Age [1]	1.381	0.349	15.664	1	0.000	3.978
DADLs[2]	1.397	0.350	15.924	1	0.000	4.042
Drugs[3]	1.515	0.443	11.715	1	0.001	4.547
Constant	-3.234	0.295	120.122	1	0.000	0.039

Hosmer and Lemeshow goodness of fit test p= 0.873

[1] Age: > 85 years old

[2] DADLs: Dependence in 5 or more activities of daily livings

[3] Drugs: total of 2 or more points for drugs taken on admission where antidepressants, antidementia drugs, and anticonvulsants score 1 point each, and antipsychotics score 2 points

Table 8 Logistic regression model

Group	Points on the prediction rule	Incidence of delirium (%)	OR	AUC (IC 95%)
Derivation cohort (n=397)				0.77 (0.73-0.82)
	0	9/219 (4)	Reference	
	1	16/116 (14)	3.7 (1.5-8.7)	
	≥2	27/62 (43)	18 (7.8-41.5)	
Validation cohort (n=302)				0.85 (0.8-0.88)
	0	5/142 (3.5)	Reference	
	1	18/77 (23)	8.3 (2.9-23.6)	
	≥2	53/83 (64)	48.4 (17.8-131.4)	

Table 9 A 2 X 2 table for the validation cohort

Cut-off point	Delirium	No delirium	Total
0 (negative)	5	137	142
≥1 (positive)	71	89	160
	76	226	302

Sensitivity = 93.4%, 95% CI 85.5 to 97.2

Specificity = 60.6%, 95% CI 54.1 to 66.8

PPV = 44.4%, 95% CI 36.9 to 52.1

NPV = 96.5%, 95% CI 92 to 98.5

Figure 1: ROC curve for the derivation cohort

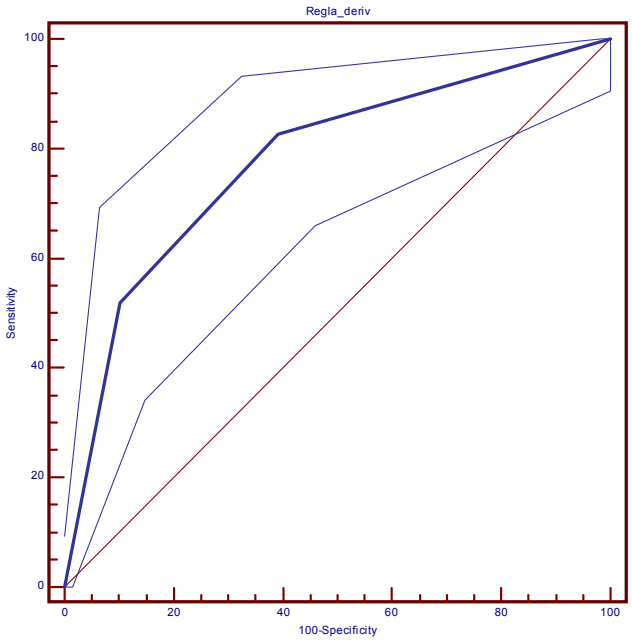
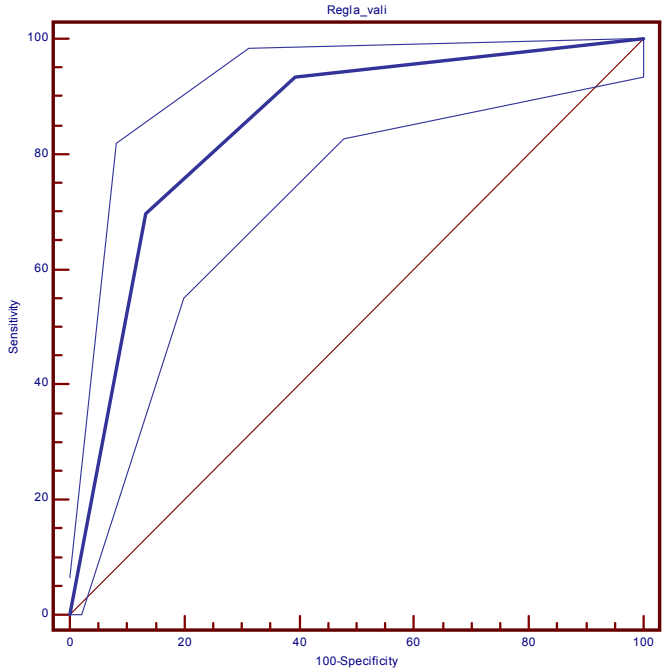


Figure 2: ROC curve for the validation cohort



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.