



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-001599
Article Type:	Research
Date Submitted by the Author:	01-Jun-2012
Complete List of Authors:	Urreta, Iratxe Emparanza, Jose Ignacio; Osakidetza, Martinez, Juan Antonio Basabe, Iban; Osakidetza, Belastegui, Ana; Osakidetza, Aguirre, Cristina; Osakidetza, Goikoetxea, Xabier; Osakidetza, Liceaga, Nerea; osakidetza,
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Neurology
Keywords:	Delirium, clinical prediction rule, elderly

SCHOLARONE™
Manuscripts

1
2
3 **DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR**
4 **DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN**
5 **OBSERVATIONAL STUDY.**
6
7
8
9

10
11
12
13 J Martinez RN¹, A Belastegui RN¹, I Basabe MD¹, X Goicoechea MD¹, C Agirre
14 MD¹, N Lizeaga RN¹, I Urreta MD², JI Emparanza MD³.
15
16
17

18 ¹ Dept. of Internal Medicine, Donostia University Hospital, Spain
19

20
21 ² Clinical Epidemiology Unit, Critical Appraisal Skills Programme – Spain
22 (CASPe), Donostia University Hospital, Spain
23
24

25
26 ³ Clinical Epidemiology Unit, CIBER-ESP & CASPe, Donostia University
27 Hospital, Spain
28
29
30
31

32
33
34
35 Corresponding author:
36

37
38 I Urreta
39

40
41 Email: IRATXE.URRETABARALLOBRE@OSAKIDETZA.NET
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Copyright

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.”

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 antimentia 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 \geq 85, high level of dependence, and being on psychotropic medication). The result is considered positive if the score is \geq 1. The rule accuracy was: sensitivity = 93.4% (95% CI: 85.5-97.2),

1
2
3 specificity = 60.6% (95% CI: 54.1-66.8), PPV = 44.4% (95% CI: 36.9-52.1), and
4
5 NPV = 96.5% (95% CI: 92-98.5). The area under the ROC curve was 0.85 for
6
7 the validation cohort.
8
9

10 **Conclusions:** The presence or absence of any of the three predictive factors
11 (age \geq 85, high level of dependence, and psychotropic medication) allowed us to
12 classify patients on internal medicine wards according to the risk of developing
13 delirium. The simplicity of the variables in our clinical prediction rule means that
14 the data collection required is feasible in busy medicine units.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 mortality⁵ and reduces the functional status of patients,⁶ as well as increasing the length of hospital stays⁷⁻⁸ 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 delirium²¹ 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).

1
2
3 The objective of this study was to derive and validate a simple clinical prediction
4 rule, based on variables that are easily measurable and are often routinely
5 taken on admission, to identify patients at high risk of developing delirium during
6 their hospital stay on an internal medicine ward.
7
8
9
10

11
12 The identification of these patients will allow us to introduce the necessary
13 preventative measures.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 diagnosis of delirium required the presence of 1) and 2), and either 3) or 4) (or
4
5 both). This assessment was performed by two independent researchers, when
6
7 it was considered that patients were ready for discharge, after analysis of any
8
9 relevant data in their medical record and nursing report. Disagreements were
10
11 resolved by consensus with a third researcher. All these evaluators were
12
13 blinded to the potential predictive variables.
14
15

16 17 18 19 20 *Potential predictors* 21

22
23 The potential predictive variables for delirium were selected after a systematic
24
25 review of the literature^{10-14 23-25}. We sought to identify variables that were easy
26
27 to measure and are often routinely recorded on admission to these wards.
28
29

30
31 The following variables were selected and measured on admission: age (years),
32
33 sex, systolic blood pressure (mmHg), heart rate (beats/min), respiratory rate
34
35 (breaths/minute), axillary temperature (°C), oxygen therapy (no: not used; and
36
37 yes: oxygen with nasal cannula, mask, and/or oxygen at home), fluid therapy,
38
39 presence of urinary catheter, level of consciousness (normal: alert; or altered:
40
41 drowsiness, unresponsiveness to voice, unresponsiveness to pain, and/or
42
43 generally unresponsive), diagnosis of infection at admission (respiratory, urinary
44
45 or other types of infections; or no infection: any other cause of admission),
46
47 admission in the previous year, admission in the previous month, hearing
48
49 impairment (use of a hearing aid, or deafness reported by the patient or
50
51 caregiver), vision impairment (regular use of glasses or reduction in visual
52
53 acuity reported by the patient or caregiver), and dementia (in a medical report or
54
55 reported by the caregiver). In addition, blood tests were taken on admission to
56
57
58
59
60

1
2
3 measure the following: haematocrit (%), levels of urea (mg/dl), creatinine
4 (mg/dl), sodium (mEq/l), potassium (mEq/l), and glucose (mg/dl), as well as
5
6
7 white blood cell ($10^3/\mu\text{l}$) and neutrophil ($10^3/\mu\text{l}$) counts. Lastly, certain
8
9
10 characteristics of patients prior to admission were also assessed: level of
11
12 dependence for activities of daily living (personal hygiene and grooming,
13
14 dressing and undressing, getting onto or off toilet, ambulation, bowel and
15
16 bladder control, and self-feeding) as dichotomous variables (dependent;
17
18 independent); presence of pressure ulcers, and excess alcohol intake (>60
19
20 g/ethanol/day), as well as use of certain types of medication: benzodiazepines,
21
22 antidepressants, antidementia drugs, antipsychotics, anti-Parkinson's drugs, or
23
24 anticonvulsants.
25
26
27
28
29
30

31 *Statistical analysis*

32
33
34 A descriptive analysis was carried out, based on the calculation of means and
35
36 standard deviations for continuous variables, and absolute or relative
37
38 frequencies as percentages for categorical variables. Subsequently, some
39
40 continuous variables were dichotomised using the median value.
41
42
43
44
45
46

47 *Sample size*

48
49 Assuming a prevalence of delirium at admission of 10%, it was calculated that
50
51 we needed 10 patients with delirium for each variable included in the model,
52
53
54 with the intention that the model should be as parsimonious as possible.
55
56
57
58
59
60

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

1
2
3 lowest risk category as the reference. The performance of the rule in the two
4
5 cohorts was explored using ROC curve analysis.
6
7

8 To assess the diagnostic accuracy of the rule, we constructed a 2x2 table for
9
10 calculation of the following: sensitivity, specificity, and positive and negative
11
12 predictive values. The 95% confidence intervals of these indicators were also
13
14 calculated assuming a binomial distribution.
15
16

17
18 We used SPSS 19.0 and MedCalc for all the analysis.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 of 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, antimentia, or anticonvulsant drug contributing equally, while antipsychotic drugs were weighted by a factor of two. The

1
2
3 activities of daily living data were also dichotomised with a cut-off of reported
4
5 impairments in five activities.
6
7

8 The scores for the clinical prediction rule were assigned on the basis of
9
10 regression coefficients obtained in the logistic regression model (Table 7). One
11
12 point was given to patients older than 85 years, to those who had 2 or more
13
14 points in the variable drugs, and to those with impairments in five or more of the
15
16 activities of daily living considered. Therefore, the total score for the rule ranged
17
18 between 0 and 3.
19
20

21
22 Table 9 and Figures 1 and 2 describe the performance of the rule in the
23
24 derivation and validation cohorts. In both cohorts, we observed higher rates of
25
26 delirium associated with higher scores on the rule, the model having a good
27
28 predictive power for the validation cohort (area under the ROC curve, AUC =
29
30 0.85). In contrast with what would be expected, the values obtained in the
31
32 validation cohort are better than those obtained in the derivation cohort, and this
33
34 is probably related to the higher prevalence of delirium in validation group.
35
36
37

38 In particular, Table 9 lists the sensitivity (Se) and specificity (Sp), as well as the
39
40 positive and negative predictive values (PPVs and NPVs) obtained when the
41
42 rule was dichotomised as negative (a score of 0) or positive (as score of ≥ 1).
43
44 For the validation cohort, the Se, Sp, NPV, and PPV were 93.4%, 60.6%, 96%,
45
46 and 44% respectively.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 antimentia 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

1
2
3 triggering factors, in particular, medication, the presence of infection, surgery,
4
5 metabolic disorders, and water-electrolyte imbalances, among others.^{13 14 23-25}
6
7

8
9 In the present study, we have only explored variables that are readily available
10
11 on admission, in order to use the predictive rule at that stage and be able to
12
13 introduce preventative measures immediately in high-risk patients. These would
14
15 include trying to avoid triggering factors for the development of delirium (such
16
17 as changes of room/ward, unnecessary catheterisation, inadequate oral
18
19 hydration, and polypharmacy).
20

21
22 Interestingly, the factors found to be good predictors for the development of
23
24 delirium in our study (age \geq 85, high level of dependence, and being on
25
26 psychotropic medication), to some extent, indirectly reflect the severity of the
27
28 organic brain damage in patients with delirium.
29

30
31
32 Another predictive rule for delirium in this type of patients has been published
33
34 (21) but showed a significantly lower performance than that we obtained (AUC
35
36 = 0.66 [0.55-0.77] vs. AUC=0.85 [0.80-0.90] with our rule). Further, in our
37
38 opinion, it is also more difficult to apply than the rule we propose. The simplicity
39
40 of the variables included in our rule makes data collection a feasible task for
41
42 busy healthcare units.
43
44

45
46 Between 10% and 60% of patients admitted to hospital develop delirium,
47
48 depending on the type of patient, the prevalence in frail elderly patients being at
49
50 the top of this range. In our study, it was 13% and 25% in the derivation and
51
52 validations cohorts, respectively. Delirium is well known to be difficult to
53
54 diagnose and a wide range of instruments have been developed to help detect
55
56 the condition (26,27). We used the Confusion Assessment Method²² that has a
57
58
59

1
2
3 sensitivity of 96% (95% CI 80-100%) and a specificity of 93% (95% CI 84-
4
5 100%). In our study, the doctors in charge of the diagnosis of delirium were
6
7 specialists in internal medicine, with considerable training and experience in the
8
9 management of this type of patients, any differences being resolved by
10
11 consensus with a third specialist. We note, however, that the diagnoses of
12
13 delirium were not confirmed by a psychiatrist. This may partially explain the low
14
15 prevalence of delirium in our patients, that is, it may be that only the most
16
17 clinically striking cases, those which required pharmacological treatment, were
18
19 recognised.
20
21

22
23 The association between delirium and an increase of morbidity and mortality^{5 6 9}
24
25 is well known, as are the effectiveness of preventive measures to avoid the
26
27 development of the disease.¹⁵⁻¹⁸ The use of the proposed predictive rule would
28
29 allow us to classify around half of our inpatients (53%) as high-risk. Taking
30
31 preventative measures in this high risk group, up to 93.4% of those who
32
33 developed delirium in our study would have been covered by the measures and
34
35 might not have then developed the condition.
36
37

38
39 It would interesting for the clinical predictive rule we propose to be validated in
40
41 other cohorts of frail elderly patients with worsening of multiple medical
42
43 conditions to check its external validity.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **ACKNOWLEDGEMENTS:** We would like to thank all the medical and nursing
4 staff of the Department of Internal Medicine at Donostia University Hospital for
5 their contribution to the study.
6
7
8

9
10 **CONTRIBUTORS:** JM, AB, JIE and IU participated in the design of the study.
11 JM, AB, IB, XG, CA and NL collected all data. JIE and IU carried out the
12 statistical analysis. JM, IU and JIE drafted the manuscript. All authors approved
13 the final version to be published. IU and JM are the guarantors.
14
15
16

17
18 **COMPETING INTERESTS:** All authors have completed the Unified Competing
19 interests form at http://www.icmje.org/coi_disclosure.pdf (available on request
20 from the corresponding author) and declare: no support from any organisation
21 for the submitted work; no financial relationships with any organisations that
22 might have an interest in the submitted work in the previous three years; and no
23 other relationships or activities that could appear to have influenced the
24 submitted work.
25
26
27
28
29
30
31
32
33
34

35 **ETHICAL APPROVAL:** The design was evaluated and then approved by the
36 Clinical Research Ethics Committee of the Gipuzkoa Health region.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES:

- 1) Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing*. 2009; 38: 19-26
- 2) Trzepacz PT. Delirium. Advances in diagnosis, pathophysiology, and treatment. *Psychiatric Clinics of North America* 1996; 19 (3): 429-448.
- 3) Leentjens AF, van der Mast RC. Delirium in elderly people: an update. *Curr Opin Psychiatry*. 2005 May; 18 (3): 325-330.
- 4) Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010; 304: 443-451.
- 5) McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Archives of Internal Medicine* 2002; 162 (4): 457-463.
- 6) Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; 351 (9106): 857-861.
- 7) McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? *Journal of the American Geriatrics Society* 2003 51 (11):1539-1546.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

8) Stevens LE, de Moore GM, Simpson JM. Delirium in hospital: does it increase length of stay? Australian & New Zealand Journal of Psychiatry 1998; 32 (6): 805-808.

9) Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. Journal of General Internal Medicine 1998; 13: 234-242.

10) Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. Journal of Geriatric Psychiatry & Neurology 1998; 11 (3): 118-125; discussion 157-158.

11) Fick DM; Agostini JV; Inouye SK. Delirium superimposed on dementia: a systematic review. J Am Geriatr Soc 2002; 50 (10):1723-1732.

12) Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA. 1996; 275 (11): 852-857.

13) Laurila JV, Laakkonen ML, Tilvis RS, Pitkala KH. Predisposing and precipitating factors for delirium in a frail geriatric population. J Psychosom Res. 2008 Sep; 65 (3): 249-254.

14) Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for intensive care delirium: a systematic review. Intensive Crit Care Nurs. 2008 Apr; 24 (2):98-107.

- 1
2
3 15) Inouye, S, Bogardus, ST, Charpentier, PA, et al. A multicomponent
4 intervention to prevent delirium in hospitalized older patients. *N Engl J Med*
5 1999; 340: 669-676.
6
7
8
9
10 16) Milisen K, Lemiengre J, Braes T, Foreman M D. Multicomponent
11 intervention strategies for managing delirium in hospitalized older people:
12 systematic review. *Journal of Advanced Nursing* 2005; 52 (1): 79-90
13
14
15
16
17
18 17) Vidan MT, Sanchez E, Alonso M, Montero B, Ortiz J, Serra JA. An
19 Intervention Integrated into Daily Clinical Practice Reduces the Incidence of
20 Delirium During Hospitalization in Elderly Patients. *J Am Geriatr Soc* 2009;
21 57:2029–2036.
22
23
24
25
26 18) Siddiqi N, Holt R, Britton AM, Holmes J. Interventions for preventing
27 delirium in hospitalised patients. *Cochrane Database of Systematic Reviews*
28 2007, Issue 2. Art. No.: CD005563. DOI: 10.1002/14651858.CD005563.pub2.
29
30
31
32
33 19) Leslie DL, Marcantonio ER, Zhang Y, Summer LLs, Intuye SK. One-Year
34 Health Care Costs Associated With Delirium in the Elderly Population. *Arch*
35 *Intern Med.* 2008;168 (1):27-32
36
37
38
39 20) Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and
40 suggested modifications of methodological standards. *JAMA.* 1997 Feb 12; 277
41 (6):488-494.
42
43
44
45
46
47
48 21) Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model
49 for delirium in hospitalized elderly medical patients based on admission
50 characteristics. *Ann Intern Med.* 1993 Sep 15; 119 (6): 474-481.
51
52
53
54
55
56
57
58
59
60

1
2
3 22) Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI.
4 Clarifying confusion: the confusion assessment method. A new method for
5 detection of delirium. *Ann Intern Med.* 1990 Dec 15;113 (12):941-948.
6
7
8

9
10
11 23) Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly
12 hospitalized patients. *J Gen Intern Med.* 1998 Mar; 13 (3):204-212.
13
14

15
16 24) Pisani, MA, Murphy, TE, Van Ness, PH, et al. Characteristics associated
17 with delirium in older patients in a medical intensive care unit. *Arch Intern Med*
18 2007; 167:1629-1634.
19
20
21

22
23 25) McCusker, J, Cole, M, Abrahamowicz, M, et al. Environmental risk factors
24 for delirium in hospitalized older people. *J Am Geriatr Soc* 2001; 49:1327-1334.
25
26
27

28
29 26) Camilla L. Wong, MD, Jayna Holroyd-Leduc, MD, FRCPC, David L. Simel,
30 MD, MHS, Sharon E. Straus, MD, MSc, FRCPC. Does This Patient Have
31 Delirium? Value of Bedside Instruments. *JAMA.* 2010; 304 (7): 779-786
32
33
34
35

36
37 27) Moraga AV, Rodriguez-Pascual C. Acurate diagnosis of delirium in elderly
38 patients. *Curr Opin Psychiatry.* 2007 May; 20 (3):262-267.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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/ μ l)	12.1 (12.2)	10.1(4.7)	N.S
Neutrophils (10e3/ μ l)	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

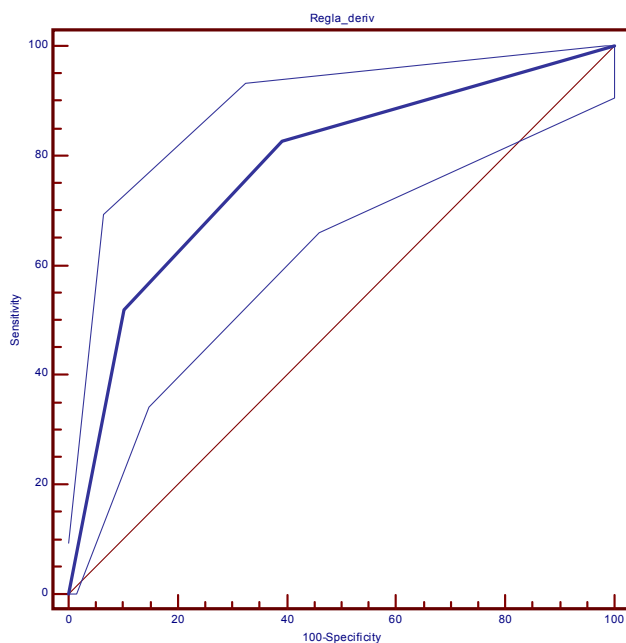
Sensitivity = 93.4%, 95% CI 85.5 to 97.2

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

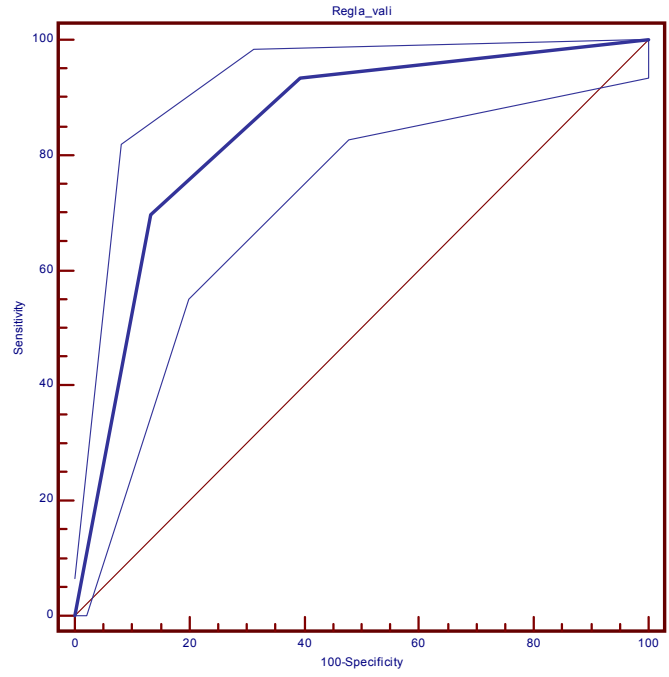


er review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 2: ROC curve for the validation cohort



review only

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>.



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-001599.R1
Article Type:	Research
Date Submitted by the Author:	16-Jul-2012
Complete List of Authors:	Urreta, Iratxe Emparanza, Jose Ignacio; Osakidetza, Martinez, Juan Antonio Basabe, Iban; Osakidetza, Belastegui, Ana; Osakidetza, Aguirre, Cristina; Osakidetza, Goikoetxea, Xabier; Osakidetza, Liceaga, Nerea; osakidetza,
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Neurology
Keywords:	Delirium, clinical prediction rule, elderly

SCHOLARONE™
Manuscripts

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>.

1
2
3
4
5
6 **DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR**
7 **DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN**
8 **OBSERVATIONAL STUDY.**
9
10

11
12
13
14
15 J Martinez RN¹, A Belastegui RN¹, I Basabe MD¹, X Goicoechea MD¹, C Agirre
16 MD¹, N Lizeaga RN¹, I Urreta MD², JI Emparanza [PhMD](#)³.
17
18

19
20 ¹ Dept. of Internal Medicine, Donostia University Hospital, Spain
21

22
23 ² Clinical Epidemiology Unit, Critical Appraisal Skills Programme – Spain
24 (CASPe), Donostia University Hospital, Spain
25

26
27 ³ Clinical Epidemiology Unit, CIBER-ESP & CASPe, Donostia University
28 Hospital, Spain
29
30

31
32
33
34 Corresponding author:
35

36
37 I Urreta
38

39
40 Email: iratxe.urretabarallobre@osakidetza.net
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1

Copyright

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) ~~licene~~license any third party to do any or all of the above.”

1
2
3
4
5
6
7 **~~What is already known on this topic~~**

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

10
11
12
13 ~~The rules published so far have limited applicability in a busy medicine unit.~~

14
15
16 **~~What this study adds~~**

17
18
19 ~~A new clinical prediction rule for delirium has been developed and validated.~~

20
21
22 ~~This is a simple clinical prediction rule based on easily measurable variables.~~

23
24
25 ~~This rule may facilitate early identification of high risk patients and target early~~
26 ~~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 antimentia 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 \geq 85, high level of dependence, and being on psychotropic medication). The result is considered positive if the score is \geq 1. The rule accuracy was: sensitivity = 93.4% (95% CI: 85.5-97.2),

1
2
3
4
5
6 specificity = 60.6% (95% CI: 54.1-66.8), PPV = 44.4% (95% CI: 36.9-52.1), and
7
8 NPV = 96.5% (95% CI: 92-98.5). The area under the ROC curve was 0.85 for
9
10 the validation cohort.

11
12 **Conclusions:** The presence or absence of any of the three predictive factors
13
14 (age \geq 85, high level of dependence, and psychotropic medication) allowed us to
15
16 classify patients on internal medicine wards according to the risk of developing
17
18 delirium. The simplicity of the variables in our clinical prediction rule means that
19
20 the data collection required is feasible in busy medicine units.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 mortality⁵ and reduces the functional status of patients,⁶ as well as increasing the length of hospital stays⁷⁻⁸ 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 delirium²¹ 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).

1
2
3
4
5
6 The objective of this study was to derive and validate a simple clinical prediction
7 rule, based on variables that are easily measurable and are often routinely
8 taken on admission, to identify patients at high risk of developing delirium during
9 their hospital stay on an internal medicine ward.
10
11
12

13
14 The identification of these patients will allow us to introduce the necessary
15 preventative measures.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

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.

Formatted: Line spacing: Double

Formatted: Font: 12 pt

Assessment of delirium

We defined delirium using the short version of the Confusion Assessment Method₁-(22)²²; a short form for assessing confusion. This diagnostic algorithm assesses four characteristics: 1) acute onset and fluctuating course, 2)

8

1
2
3
4
5
6 inattention, 3) disorganised thinking, and 4) altered level of consciousness. The
7
8 diagnosis of delirium required the presence of 1) and 2), and either 3) or 4) (or
9
10 both). This assessment was performed by two independent researchers, when
11
12 it was considered that patients were ready for discharge, after analysis of any
13
14 relevant data in their medical record and nursing report. Disagreements were
15
16 resolved by consensus with a third researcher. All these evaluators were
17
18 blinded to the potential predictive variables selected for the study.

21 22 23 *Potential predictors*

24
25
26 The potential predictive variables for delirium were selected after a systematic
27
28 review of the literature^{10-14 23-25}. We sought to identify variables that were easy
29
30 to measure and are often routinely recorded on admission to these wards.

31
32 The following variables were selected and measured on admission: age (years),
33
34 sex, systolic blood pressure (mmHg), heart rate (beats/min), respiratory rate
35
36 (breaths/minute), axillary temperature (°C), oxygen therapy (no: not used; and
37
38 yes: oxygen with nasal cannula, mask, and/or oxygen at home), fluid therapy,
39
40 presence of urinary catheter, level of consciousness (normal: alert; or altered:
41
42 drowsiness, unresponsiveness to voice, unresponsiveness to pain, and/or
43
44 generally unresponsive), diagnosis of infection at admission (respiratory, urinary
45
46 or other types of infections; or no infection: any other cause of admission),
47
48 admission in the previous year, admission in the previous month, hearing
49
50 impairment (use of a hearing aid, or deafness reported by the patient or
51
52 caregiver), vision impairment (regular use of glasses or reduction in visual
53
54 acuity reported by the patient or caregiver), and dementia (in a medical report or

55
56
57
58
59
60
9

1
2
3
4
5
6 reported by the caregiver). In addition, blood tests were taken on admission to
7
8 measure the following: haematocrit (%), levels of urea (mg/dl), creatinine
9
10 (mg/dl), sodium (mEq/l), potassium (mEq/l), and glucose (mg/dl), as well as
11
12 white blood cell ($10^3/\mu\text{l}$) and neutrophil ($10^3/\mu\text{l}$) counts. Lastly, certain
13
14 characteristics of patients prior to admission were also assessed: level of
15
16 dependence for activities of daily living (personal hygiene and grooming,
17
18 dressing and undressing, getting onto or off toilet, ambulation, bowel and
19
20 bladder control, and self-feeding) as dichotomous variables (dependent;
21
22 independent); presence of pressure ulcers, and excess alcohol intake (>60
23
24 g/ethanol/day), as well as use of certain types of medication: benzodiazepines,
25
26 antidepressants, antidementia drugs, antipsychotics, anti-Parkinson's drugs, or
27
28 anticonvulsants.
29
30
31
32

33 *Statistical analysis*

34
35
36 A descriptive analysis was carried out, based on the calculation of means and
37
38 standard deviations for continuous variables, and absolute or relative
39
40 frequencies as percentages for categorical variables. Subsequently, some
41
42 continuous variables were dichotomised using the median value.
43
44

45 *Sample size*

46
47 Assuming a prevalence of delirium at admission of 10%, it was calculated that
48
49 we needed 10 patients with delirium for each variable included in the model,
50
51 with the intention that the model should be as parsimonious as possible.
52
53
54
55

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

1
2
3
4
5
6 lowest risk category as the reference. The performance of the rule in the two
7
8 cohorts was explored using ROC curve analysis.
9

10 To assess the diagnostic accuracy of the rule, we constructed a 2x2 table for
11
12 calculation of the following: sensitivity, specificity, and positive and negative
13
14 predictive values. The 95% confidence intervals of these indicators were also
15
16 calculated assuming a binomial distribution.
17

18
19 We used SPSS 19.0 and MedCalc for all the analysis.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

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, antedementia, or anticonvulsant drug contributing equally, while antipsychotic drugs were weighted by a factor of two. The

1
2
3
4
5
6 activities of daily living data were also dichotomised with a cut-off of reported
7 impairments in five activities.
8

9
10 The scores for the clinical prediction rule were assigned on the basis of
11 regression coefficients obtained in the logistic regression model (Table 7). One
12 point was given to patients older than 85 years, to those who had 2 or more
13 points in the variable drugs, and to those with impairments in five or more of the
14 activities of daily living considered. Therefore, the total score for the rule ranged
15 between 0 and 3.
16
17
18
19
20
21

22
23 The patients with delirium of the two cohorts scored similarly: 17% and 7%
24 scored 0, 48% and 30% scored ≤ 1 and 85% and 85% scored ≤ 2 in the
25 derivation and validation cohort respectively.
26
27
28
29
30
31

Formatted: Font: 12 pt

Formatted: Line spacing: Double

32 Table 9 and Figures 1 and 2 describe the performance of the rule in the
33 derivation and validation cohorts. In both cohorts, we observed higher rates of
34 delirium associated with higher scores on the rule, the model having a good
35 predictive power for the validation cohort (area under the ROC curve, AUC =
36 0.85). In contrast with what would be expected, the values obtained in the
37 validation cohort are better than those obtained in the derivation cohort, and this
38 is probably related to the higher prevalence of delirium in validation group.
39
40
41
42
43
44
45

46 In particular, Table 9 lists the sensitivity (Se) and specificity (Sp), as well as the
47 positive and negative predictive values (PPVs and NPVs) obtained when the
48 rule was dichotomised as negative (a score of 0) or positive (as score of ≥ 1).
49 For the validation cohort, the Se, Sp, NPV, and PPV were 93.4%, 60.6%, 96%,
50 and 44% respectively
51
52
53
54
55

56 14
57
58
59
60

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.~~

15

Formatted: Left

Formatted: Font: 12 pt

Formatted: Font: 12 pt

1
2
3
4
5
6 There are multiple factors for the development of delirium, the predisposing and
7 triggering factors being well defined. The predisposing factors are mostly
8 related to degenerative brain disease (dementia, arteriosclerosis, Parkinson's
9 disease, and depression).^{10 11} On the other hand, there are a diverse range of
10 triggering factors, in particular, medication, the presence of infection, surgery,
11 metabolic disorders, and water-electrolyte imbalances, among others.^{13 14 23-25}
12
13
14
15
16
17

18 In the present study, we have only explored variables that are readily available
19 on admission, in order to use the predictive rule at that stage and be able to
20 introduce preventative measures immediately in high-risk patients. These would
21 include trying to avoid triggering factors for the development of delirium (such
22 as changes of room/ward, unnecessary catheterisation, inadequate oral
23 hydration, and polypharmacy).
24
25
26
27
28
29
30

31 Interestingly, the factors found to be good predictors for the development of
32 delirium in our study (age \geq 85, high level of dependence, and being on
33 psychotropic medication), to some extent, indirectly reflect the severity of the
34 organic brain damage in patients with delirium.
35
36
37
38

39 Another predictive rule for delirium in this type of patients has been published²¹
40 ~~(21)~~ but showed a significantly lower performance than that we obtained (AUC
41 = 0.66 [0.55-0.77] vs. AUC=0.85 [0.80-0.90] with our rule). Further, in our
42 opinion, it is also more difficult to apply than the rule we propose. The simplicity
43 of the variables included in our rule makes data collection a feasible task for
44 busy healthcare units.
45
46
47
48
49
50
51

52 Between 10% and 60% of patients admitted to hospital develop delirium,
53 depending on the type of patient, the prevalence in frail elderly patients being at
54
55

56
57
58
59
60

16

1
2
3
4
5
6 the top of this range. In our study, it was 13% and 25% in the derivation and
7
8 validations cohorts, respectively. Delirium is well known to be difficult to
9
10 diagnose and a wide range of instruments have been developed to help detect
11 the condition.^{26 27} ~~(26,27)~~ We used the Confusion Assessment Method²² that
12
13 has a sensitivity of 96% (95% CI 80-100%) and a specificity of 93% (95% CI 84-
14
15 100%). In our study, the doctors in charge of the diagnosis of delirium were
16
17 specialists in internal medicine, with considerable training and experience in the
18
19 management of this type of patients, any differences being resolved by
20
21 consensus with a third specialist. We note, however, that the diagnoses of
22
23 delirium were not confirmed by a psychiatrist. This may partially explain the low
24
25 prevalence of delirium in our patients, that is, it may be that only the most
26
27 clinically striking cases, those which required pharmacological treatment, were
28
29 recognised.
30

31
32 The association between delirium and an increase of morbidity and mortality^{5 6 9}
33
34 is well known, as are the effectiveness of preventive measures to avoid the
35
36 development of the disease.¹⁵⁻¹⁸ The use of the proposed predictive rule would
37
38 allow us to classify around half of our inpatients (53%) as high-risk. Taking
39
40 preventative measures in this high risk group, up to 93.4% of those who
41
42 developed delirium in our study would have been covered by the measures and
43
44 might not have then developed the condition.
45

46
47 It would be interesting for the clinical predictive rule we propose to be validated
48
49 in other cohorts of frail elderly patients with worsening of multiple medical
50
51 conditions to check its external validity.
52
53
54
55

1
2
3
4
5
6 **ACKNOWLEDGEMENTS:** We would like to thank all the medical and nursing
7
8 staff of the Department of Internal Medicine at Donostia University Hospital for
9
10 their contribution to the study.

11
12 **CONTRIBUTORS:** JM, AB, JIE and IU participated in the design of the study.
13
14 JM, AB, IB, XG, CA and NL collected all data. JIE and IU carried out the
15
16 statistical analysis. JM, IU and JIE drafted the manuscript. All authors approved
17
18 the final version to be published. IU and JM are the guarantors.

19
20
21 **COMPETING INTERESTS:** All authors have completed the Unified Competing
22
23 interests form at http://www.icmje.org/coi_disclosure.pdf (available on request
24
25 from the corresponding author) and declare: no support from any organisation
26
27 for the submitted work; no financial relationships with any organisations that
28
29 might have an interest in the submitted work in the previous three years; and no
30
31 other relationships or activities that could appear to have influenced the
32
33 submitted work.

34
35 **ETHICAL APPROVAL:** The design was evaluated and then approved by the
36
37 Clinical Research Ethics Committee of the Gipuzkoa Health region.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

REFERENCES:

1) Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing*. 2009; 38: 19-26

2) Trzepacz PT. Delirium. *Advances in diagnosis, pathophysiology, and treatment*. *Psychiatric Clinics of North America* 1996; 19 (3): 429-448.

3) Leentjens AF, van der Mast RC. Delirium in elderly people: an update. *Curr Opin Psychiatry*. 2005 May; 18 (3): 325-330.

4) Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010; 304: 443-451.

5) McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Archives of Internal Medicine* 2002; 162 (4): 457-463.

6) Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. *International Study of Post-Operative Cognitive Dysfunction*. *Lancet* 1998; 351 (9106): 857-861.

7) McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? *Journal of the American Geriatrics Society* 2003 51 (11):1539-1546.

19

1
2
3
4
5
6
7
8 8) Stevens LE, de Moore GM, Simpson JM. Delirium in hospital: does it
9 increase length of stay? Australian & New Zealand Journal of Psychiatry 1998;
10 32 (6): 805-808.
11
12

13
14
15
16 9) Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium
17 contribute to poor hospital outcomes? A three-site epidemiologic study. Journal
18 of General Internal Medicine 1998; 13: 234-242.
19

20
21
22
23
24 10) Inouye SK. Delirium in hospitalized older patients: recognition and risk
25 factors. Journal of Geriatric Psychiatry & Neurology 1998; 11 (3): 118-125;
26 discussion 157-158.
27

28
29
30 11) Fick DM; Agostini JV; Inouye SK. Delirium superimposed on dementia: a
31 systematic review. J Am Geriatr Soc 2002; 50 (10):1723-1732.
32

33
34
35 12) Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized
36 elderly persons. Predictive model and interrelationship with baseline
37 vulnerability. JAMA. 1996; 275 (11): 852-857.
38

39
40
41 13) Laurila JV, Laakkonen ML, Tilvis RS, Pitkala KH. Predisposing and
42 precipitating factors for delirium in a frail geriatric population. J Psychosom
43 Res. 2008 Sep; 65 (3): 249-254.
44
45

46
47
48 14) Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S,
49 Bossaert L. Risk factors for intensive care delirium: a systematic review.
50 Intensive Crit Care Nurs. 2008 Apr; 24 (2):98-107.
51

52
53
54
55
56
57 20
58
59
60

1
2
3
4
5
6 15) Inouye, S, Bogardus, ST, Charpentier, PA, et al. A multicomponent
7 intervention to prevent delirium in hospitalized older patients. *N Engl J Med*
8 1999; 340: 669-676.
9

10
11
12 16) Milisen K, Lemiengre J, Braes T, Foreman M D. Multicomponent
13 intervention strategies for managing delirium in hospitalized older people:
14 systematic review. *Journal of Advanced Nursing* 2005; 52 (1): 79-90
15
16

17
18
19 17) Vidan MT, Sanchez E, Alonso M, Montero B, Ortiz J, Serra JA. An
20 Intervention Integrated into Daily Clinical Practice Reduces the Incidence of
21 Delirium During Hospitalization in Elderly Patients. *J Am Geriatr Soc* 2009;
22 57:2029–2036.
23
24

25
26
27 18) Siddiqi N, Holt R, Britton AM, Holmes J. Interventions for preventing
28 delirium in hospitalised patients. *Cochrane Database of Systematic Reviews*
29 2007, Issue 2. Art. No.: CD005563. DOI: 10.1002/14651858.CD005563.pub2.
30
31

32
33 19) Leslie DL, Marcantonio ER, Zhang Y, Summer LLs, Intuye SK. One-Year
34 Health Care Costs Associated With Delirium in the Elderly Population. *Arch*
35 *Intern Med.* 2008;168 (1):27-32
36
37

38
39 20) Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and
40 suggested modifications of methodological standards. *JAMA.* 1997 Feb 12; 277
41 (6):488-494.
42
43

44
45
46 21) Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model
47 for delirium in hospitalized elderly medical patients based on admission
48 characteristics. *Ann Intern Med.* 1993 Sep 15; 119 (6): 474-481.
49
50

51
52
53
54
55
56
57 21
58
59
60

1
2
3
4
5
6 22) Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI.
7 Clarifying confusion: the confusion assessment method. A new method for
8 detection of delirium. *Ann Intern Med.* 1990 Dec 15;113 (12):941-948.
9

10
11
12
13 23) Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly
14 hospitalized patients. *J Gen Intern Med.* 1998 Mar; 13 (3):204-212.
15
16

17
18 24) Pisani, MA, Murphy, TE, Van Ness, PH, et al. Characteristics associated
19 with delirium in older patients in a medical intensive care unit. *Arch Intern Med*
20 2007; 167:1629-1634.
21
22

23
24 25) McCusker, J, Cole, M, Abrahamowicz, M, et al. Environmental risk factors
25 for delirium in hospitalized older people. *J Am Geriatr Soc* 2001; 49:1327-1334.
26
27

28
29 26) Camilla L. Wong, MD, Jayna Holroyd-Leduc, MD, FRCPC, David L. Simel,
30 MD, MHS, Sharon E. Straus, MD, MSc, FRCPC. Does This Patient Have
31 Delirium? Value of Bedside Instruments. *JAMA.* 2010; 304 (7): 779-786
32
33

34
35
36 27) Moraga AV, Rodriguez-Pascual C. Acurate diagnosis of delirium in elderly
37 patients. *Curr Opin Psychiatry.* 2007 May; 20 (3):262-267.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57

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/ μ l)	12.1 (12.2)	10.1(4.7)	N.S
Neutrophils (10e3/ μ l)	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, antedementia drugs, and anticonvulsants score 1 point each, and antipsychotics score 2 points

Formatted: Font: (Default) Arial

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

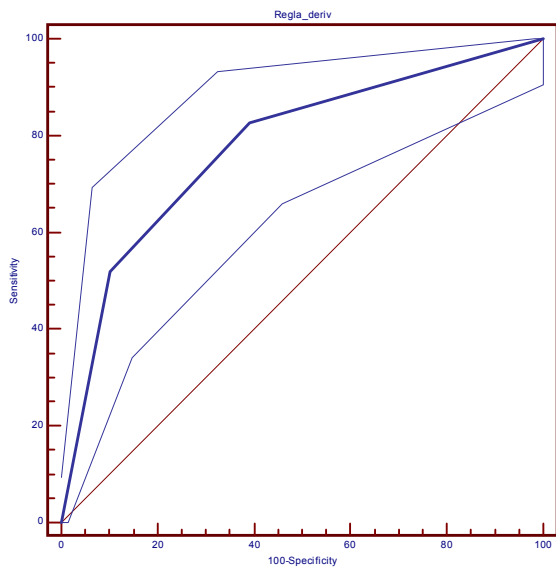
Sensitivity = 93.4%, 95% CI 85.5 to 97.2

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

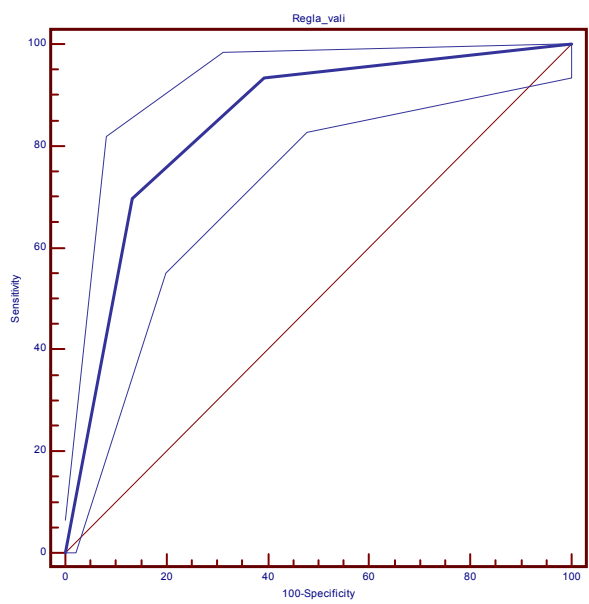
Figure 1: ROC curve for the derivation cohort



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 2: ROC curve for the validation cohort



review only



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-001599.R2
Article Type:	Research
Date Submitted by the Author:	03-Aug-2012
Complete List of Authors:	Urreta, Iratxe Emparanza, Jose Ignacio; Osakidetza, Martinez, Juan Antonio Basabe, Iban; Osakidetza, Belastegui, Ana; Osakidetza, Aguirre, Cristina; Osakidetza, Goikoetxea, Xabier; Osakidetza, Liceaga, Nerea; osakidetza,
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Neurology, Mental health
Keywords:	Delirium, clinical prediction rule, elderly

SCHOLARONE™
Manuscripts

1
2
3 **DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR**
4 **DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN**
5 **OBSERVATIONAL STUDY.**
6
7
8
9

10
11
12
13 J Martinez RN¹, A Belastegui RN¹, I Basabe MD¹, X Goicoechea MD¹, C Agirre
14 MD¹, N Lizeaga RN¹, I Urreta MD², JI Emparanza PhD³.
15
16

17
18 ¹ Dept. of Internal Medicine, Donostia University Hospital, Spain
19

20
21 ² Clinical Epidemiology Unit, Critical Appraisal Skills Programme – Spain
22 (CASPe), Donostia University Hospital, Spain
23

24
25 ³ Clinical Epidemiology Unit, CIBER-ESP & CASPe, Donostia University
26 Hospital, Spain
27
28
29
30
31

32
33
34
35 Corresponding author:
36

37
38 I Urreta
39

40
41 Email: iratxe.urretabarallobre@osakidetza.net
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Copyright

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) license any third party to do any or all of the above.”

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 antimentia 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 \geq 85, high level of dependence, and being on psychotropic medication). The result is considered positive if the score is \geq 1. The rule accuracy was: sensitivity = 93.4% (95% CI: 85.5-97.2),

1
2
3 specificity = 60.6% (95% CI: 54.1-66.8), PPV = 44.4% (95% CI: 36.9-52.1), and
4
5 NPV = 96.5% (95% CI: 92-98.5). The area under the ROC curve was 0.85 for
6
7 the validation cohort.
8
9

10 **Conclusions:** The presence or absence of any of the three predictive factors
11 (age \geq 85, high level of dependence, and psychotropic medication) allowed us to
12
13 classify patients on internal medicine wards according to the risk of developing
14
15 delirium. The simplicity of the variables in our clinical prediction rule means that
16
17 the data collection required is feasible in busy medicine units.
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 mortality⁵ and reduces the functional status of patients,⁶ as well as increasing the length of hospital stays⁷⁻⁸ 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 delirium²¹ 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).

1
2
3 The objective of this study was to derive and validate a simple clinical prediction
4 rule, based on variables that are easily measurable and are often routinely
5 taken on admission, to identify patients at high risk of developing delirium during
6 their hospital stay on an internal medicine ward.
7
8
9

10
11
12 The identification of these patients will allow us to introduce the necessary
13 preventative measures.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)

1
2
3 inattention, 3) disorganised thinking, and 4) altered level of consciousness. The
4 diagnosis of delirium required the presence of 1) and 2), and either 3) or 4) (or
5 both). This assessment was performed by two independent researchers, when
6 it was considered that patients were ready for discharge, after analysis of any
7 relevant data in their medical record and nursing report. Disagreements were
8 resolved by consensus with a third researcher. All these evaluators were
9 blinded to the potential predictive variables selected for the study.
10
11
12
13
14
15
16
17
18
19
20
21

22 *Potential predictors*

23
24
25 The potential predictive variables for delirium were selected after a systematic
26 review of the literature^{10-14 23-25}. We sought to identify variables that were easy
27 to measure and are often routinely recorded on admission to these wards.
28
29
30
31

32
33 The following variables were selected and measured on admission: age (years),
34 sex, systolic blood pressure (mmHg), heart rate (beats/min), respiratory rate
35 (breaths/minute), axillary temperature (°C), oxygen therapy (no: not used; and
36 yes: oxygen with nasal cannula, mask, and/or oxygen at home), fluid therapy,
37 presence of urinary catheter, level of consciousness (normal: alert; or altered:
38 drowsiness, unresponsiveness to voice, unresponsiveness to pain, and/or
39 generally unresponsive), diagnosis of infection at admission (respiratory, urinary
40 or other types of infections; or no infection: any other cause of admission),
41 admission in the previous year, admission in the previous month, hearing
42 impairment (use of a hearing aid, or deafness reported by the patient or
43 caregiver), vision impairment (regular use of glasses or reduction in visual
44 acuity reported by the patient or caregiver), and dementia (in a medical report or
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 reported by the caregiver). In addition, blood tests were taken on admission to
4
5 measure the following: haematocrit (%), levels of urea (mg/dl), creatinine
6
7 (mg/dl), sodium (mEq/l), potassium (mEq/l), and glucose (mg/dl), as well as
8
9 white blood cell ($10^3/\mu\text{l}$) and neutrophil ($10^3/\mu\text{l}$) counts. Lastly, certain
10
11 characteristics of patients prior to admission were also assessed: level of
12
13 dependence for activities of daily living (personal hygiene and grooming,
14
15 dressing and undressing, getting onto or off toilet, ambulation, bowel and
16
17 bladder control, and self-feeding) as dichotomous variables (dependent;
18
19 independent); presence of pressure ulcers, and excess alcohol intake (>60
20
21 g/ethanol/day), as well as use of certain types of medication: benzodiazepines,
22
23 antidepressants, antidementia drugs, antipsychotics, anti-Parkinson's drugs, or
24
25 anticonvulsants.
26
27
28
29
30
31
32

33 *Statistical analysis*

34
35
36 A descriptive analysis was carried out, based on the calculation of means and
37
38 standard deviations for continuous variables, and absolute or relative
39
40 frequencies as percentages for categorical variables. Subsequently, some
41
42 continuous variables were dichotomised using the median value.
43
44
45

46 *Sample size*

47
48
49 Assuming a prevalence of delirium at admission of 10%, it was calculated that
50
51 we needed 10 patients with delirium for each variable included in the model,
52
53 with the intention that the model should be as parsimonious as possible.
54
55
56
57
58
59
60

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

1
2
3 lowest risk category as the reference. The performance of the rule in the two
4
5 cohorts was explored using ROC curve analysis.
6
7

8 To assess the predictive accuracy of the rule, we constructed a 2x2 table for
9
10 calculation of the following: sensitivity, specificity, and positive and negative
11
12 predictive values. The 95% confidence intervals of these indicators were also
13
14 calculated assuming a binomial distribution.
15
16

17
18 We used SPSS 19.0 and MedCalc for all the analysis.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 of 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, antedementia, or anticonvulsant drug contributing equally, while antipsychotic drugs were weighted by a factor of two. The

1
2
3 activities of daily living data were also dichotomised with a cut-off of reported
4
5 impairments in five activities.
6
7

8 The scores for the clinical prediction rule were assigned on the basis of
9
10 regression coefficients obtained in the logistic regression model (Table 7). One
11
12 point was given to patients older than 85 years, to those who had 2 or more
13
14 points in the variable drugs, and to those with impairments in five or more of the
15
16 activities of daily living considered. Therefore, the total score for the rule ranged
17
18 between 0 and 3.
19

20
21
22 The patients with delirium of the two cohorts scored similarly: 17% and 7%
23
24 scored 0, 48% and 30% scored ≤ 1 and 85% and 85% scored ≤ 2 in the
25
26 derivation and validation cohort respectively.
27

28
29
30 Table 9 and Figures 1 and 2 describe the performance of the rule in the
31
32 derivation and validation cohorts. In both cohorts, we observed higher rates of
33
34 delirium associated with higher scores on the rule, the model having a good
35
36 predictive power for the validation cohort (area under the ROC curve, AUC =
37
38 0.85). In contrast with what would be expected, the values obtained in the
39
40 validation cohort are better than those obtained in the derivation cohort, and this
41
42 is probably related to the higher incidence of delirium in validation group.
43
44

45
46 In particular, Table 9 lists the sensitivity (Se) and specificity (Sp), as well as the
47
48 positive and negative predictive values (PPVs and NPVs) obtained when the
49
50 rule was dichotomised as negative (a score of 0) or positive (as score of ≥ 1).
51
52 For the validation cohort, the Se, Sp, NPV, and PPV were 93.4%, 60.6%, 96%,
53
54 and 44% respectively
55
56
57
58
59
60

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 antimentia 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}

1
2
3 In the present study, we have only explored variables that are readily available
4 on admission, in order to use the predictive rule at that stage and be able to
5 introduce preventative measures immediately in high-risk patients. These would
6 include trying to avoid triggering factors for the development of delirium (such
7 as changes of room/ward, unnecessary catheterisation, inadequate oral
8 hydration, and polypharmacy).

9
10
11
12
13
14
15
16
17 Interestingly, the factors found to be good predictors for the development of
18 delirium in our study (age \geq 85, high level of dependence, and being on
19 psychotropic medication), to some extent, indirectly reflect the severity of the
20 organic brain damage in patients with delirium.

21
22
23
24
25
26
27 Another predictive rule for delirium in this type of patients has been published²¹
28 but showed a significantly lower performance than that we obtained (AUC =
29 0.66 [0.55-077] vs. AUC=0.85 [0.80-0.90] with our rule). Further, in our opinion,
30 it is also more difficult to apply than the rule we propose. The simplicity of the
31 variables included in our rule makes data collection a feasible task for busy
32 healthcare units.

33
34
35
36
37
38
39
40
41 Between 10% and 60% of patients admitted to hospital develop delirium,
42 depending on the type of patient, the incidence in frail elderly patients being at
43 the top of this range. In our study, it was 13% and 25% in the derivation and
44 validations cohorts, respectively. Delirium is well known to be difficult to
45 diagnose and a wide range of instruments have been developed to help detect
46 the condition.^{26 27} We used the Confusion Assessment Method²² that has a
47 sensitivity of 96% (95% CI 80-100%) and a specificity of 93% (95% CI 84-
48 100%). In our study, the doctors in charge of the diagnosis of delirium were
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 specialists in internal medicine, with considerable training and experience in the
4 management of this type of patients, any differences being resolved by
5 consensus with a third specialist. We note, however, that the diagnoses of
6 delirium were not confirmed by a psychiatrist. This may partially explain the low
7 incidence of delirium in our patients, that is, it may be that only the most
8 clinically striking cases, those which required pharmacological treatment, were
9 recognised.
10

11
12 The association between delirium and an increase of morbidity and mortality^{5 6 9}
13 is well known, as are the effectiveness of preventive measures to avoid the
14 development of the disease.¹⁵⁻¹⁸ The use of the proposed predictive rule would
15 allow us to classify around half of our inpatients (53%) as high-risk. Taking
16 preventative measures in this high risk group, up to 93.4% of those who
17 developed delirium in our study would have been covered by the measures and
18 might not have then developed the condition.
19

20
21 It would be interesting for the clinical predictive rule we propose to be validated
22 in other cohorts of frail elderly patients with worsening of multiple medical
23 conditions to check its external validity.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **ACKNOWLEDGEMENTS:** We would like to thank all the medical and nursing
4 staff of the Department of Internal Medicine at Donostia University Hospital for
5 their contribution to the study.
6
7
8

9
10 **CONTRIBUTORS:** JM, AB, JIE and IU participated in the design of the study.
11 JM, AB, IB, XG, CA and NL collected all data. JIE and IU carried out the
12 statistical analysis. JM, IU and JIE drafted the manuscript. All authors approved
13 the final version to be published. IU and JM are the guarantors.
14
15
16

17
18 **COMPETING INTERESTS:** All authors have completed the Unified Competing
19 interests form at http://www.icmje.org/coi_disclosure.pdf (available on request
20 from the corresponding author) and declare: no support from any organisation
21 for the submitted work; no financial relationships with any organisations that
22 might have an interest in the submitted work in the previous three years; and no
23 other relationships or activities that could appear to have influenced the
24 submitted work.
25
26
27
28
29
30
31

32
33 **ETHICAL APPROVAL:** The design was evaluated and then approved by the
34 Clinical Research Ethics Committee of the Gipuzkoa Health region.
35
36
37
38

39
40
41 **DATA SHARING STATEMENT:** No additional data available
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES:

- 1) Cole MG, Ciampi A, Belzile E, et al. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing*. 2009; 38: 19-26
- 2) Trzepacz PT. Delirium. Advances in diagnosis, pathophysiology, and treatment. *Psychiatric Clinics of North America* 1996; 19 (3): 429-448.
- 3) Leentjens AF, van der Mast RC. Delirium in elderly people: an update. *Curr Opin Psychiatry*. 2005 May; 18 (3): 325-330.
- 4) Witlox J, Eurelings LS, de Jonghe JF, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010; 304: 443-451.
- 5) McCusker J, Cole M, Abrahamowicz M, et al. Delirium predicts 12-month mortality. *Archives of Internal Medicine* 2002; 162 (4): 457-463.
- 6) Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; 351 (9106): 857-861.
- 7) McCusker J, Cole MG, Dendukuri N, et al. Does delirium increase hospital stay? *Journal of the American Geriatrics Society* 2003 51 (11):1539-1546.

1
2
3 8) Stevens LE, de Moore GM, Simpson JM. Delirium in hospital: does it
4 increase length of stay? Australian & New Zealand Journal of Psychiatry 1998;
5 32 (6): 805-808.
6
7

8
9
10
11 9) Inouye SK, Rushing JT, Foreman MD, et al. Does delirium contribute to poor
12 hospital outcomes? A three-site epidemiologic study. Journal of General
13 Internal Medicine 1998; 13: 234-242.
14
15

16
17
18
19
20 10) Inouye SK. Delirium in hospitalized older patients: recognition and risk
21 factors. Journal of Geriatric Psychiatry & Neurology 1998; 11 (3): 118-125;
22 discussion 157-158.
23
24

25
26
27
28 11) Fick DM; Agostini JV; Inouye SK. Delirium superimposed on dementia: a
29 systematic review. J Am Geriatr Soc 2002; 50 (10):1723-1732.
30
31

32
33 12) Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized
34 elderly persons. Predictive model and interrelationship with baseline
35 vulnerability. JAMA. 1996; 275 (11): 852-857.
36
37

38
39
40 13) Laurila JV, Laakkonen ML, Tilvis RS, et al. Predisposing and precipitating
41 factors for delirium in a frail geriatric population. J Psychosom Res. 2008 Sep;
42 65 (3): 249-254.
43
44

45
46
47 14) Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, et al. Risk
48 factors for intensive care delirium: a systematic review. Intensive Crit Care
49 Nurs. 2008 Apr; 24 (2):98-107.
50
51

52
53
54 15) Inouye, S, Bogardus, ST, Charpentier, PA, et al. A multicomponent
55 intervention to prevent delirium in hospitalized older patients. N Engl J Med
56 1999; 340: 669-676.
57
58

1
2
3
4
5 16) Milisen K, Lemiengre J, Braes T, et al. Multicomponent intervention
6 strategies for managing delirium in hospitalized older people: systematic review.
7
8 Journal of Advanced Nursing 2005; 52 (1): 79-90
9

10
11
12 17) Vidan MT, Sanchez E, Alonso M, et al. An Intervention Integrated into Daily
13 Clinical Practice Reduces the Incidence of Delirium During Hospitalization in
14 Elderly Patients. *J Am Geriatr Soc* 2009; 57:2029–2036.
15
16
17

18
19 18) Siddiqi N, Holt R, Britton AM, et al. Interventions for preventing delirium in
20 hospitalised patients. *Cochrane Database of Systematic Reviews* 2007, Issue 2.
21 Art. No.: CD005563. DOI: 10.1002/14651858.CD005563.pub2.
22
23
24

25
26 19) Leslie DL, Marcantonio ER, Zhang Y, et al. One-Year Health Care Costs
27 Associated With Delirium in the Elderly Population. *Arch Intern Med.* 2008;168
28 (1):27-32
29
30

31
32 20) Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and
33 suggested modifications of methodological standards. *JAMA.* 1997 Feb 12; 277
34 (6):488-494.
35
36
37

38
39 21) Inouye SK, Viscoli CM, Horwitz RI, et al. A predictive model for delirium in
40 hospitalized elderly medical patients based on admission characteristics. *Ann*
41 *Intern Med.* 1993 Sep 15; 119 (6): 474-481.
42
43
44

45
46 22) Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the
47 confusion assessment method. A new method for detection of delirium. *Ann*
48 *Intern Med.* 1990 Dec 15;113 (12):941-948.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 23) Elie M, Cole MG, Primeau FJ, et al. Delirium risk factors in elderly
4 hospitalized patients. J Gen Intern Med. 1998 Mar; 13 (3):204-212.
5
6

7
8 24) Pisani, MA, Murphy, TE, et al. Characteristics associated with delirium in
9 older patients in a medical intensive care unit. Arch Intern Med 2007; 167:1629-
10 1634.
11
12

13
14 25) McCusker, J, Cole, M, Abrahamowicz, M, et al. Environmental risk factors
15 for delirium in hospitalized older people. J Am Geriatr Soc 2001; 49:1327-1334.
16
17

18
19
20 26) Camilla L. Wong, MD, Jayna Holroyd-Leduc, et al. Does This Patient Have
21 Delirium? Value of Bedside Instruments. JAMA. 2010; 304 (7): 779-786
22
23

24
25
26 27) Moraga AV, Rodriguez-Pascual C. Acurate diagnosis of delirium in elderly
27 patients. Curr Opin Psychiatry. 2007 May; 20 (3):262-267.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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/ μ l)	12.1 (12.2)	10.1(4.7)	N.S
Neutrophils (10e3/ μ l)	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

1
2
3 **DERIVATION AND VALIDATION OF A CLINICAL PREDICTION RULE FOR**
4 **DELIRIUM IN PATIENTS ADMITTED TO A MEDICAL WARD: AN**
5 **OBSERVATIONAL STUDY.**
6
7
8
9

10
11
12
13 J Martinez RN¹, A Belastegui RN¹, I Basabe MD¹, X Goicoechea MD¹, C Agirre
14 MD¹, N Lizeaga RN¹, I Urreta MD², JI Emparanza PhD³.
15
16

17
18 ¹ Dept. of Internal Medicine, Donostia University Hospital, Spain
19

20
21 ² Clinical Epidemiology Unit, Critical Appraisal Skills Programme – Spain
22 (CASPe), Donostia University Hospital, Spain
23

24
25 ³ Clinical Epidemiology Unit, CIBER-ESP & CASPe, Donostia University
26 Hospital, Spain
27
28
29
30
31

32
33
34
35 Corresponding author:
36

37
38 I Urreta
39

40
41 Email: iratxe.urretabarallobre@osakidetza.net
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Copyright

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) license any third party to do any or all of the above.”

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~~ 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 antimentia 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 \geq 85, high level of dependence, and being on psychotropic medication). The result is considered positive if the score is \geq 1. The rule accuracy was: sensitivity = 93.4% (95% CI: 85.5-97.2),

1
2
3 specificity = 60.6% (95% CI: 54.1-66.8), PPV = 44.4% (95% CI: 36.9-52.1), and
4
5 NPV = 96.5% (95% CI: 92-98.5). The area under the ROC curve was 0.85 for
6
7 the validation cohort.
8
9

10 **Conclusions:** The presence or absence of any of the three predictive factors
11 (age \geq 85, high level of dependence, and psychotropic medication) allowed us to
12 classify patients on internal medicine wards according to the risk of developing
13 delirium. The simplicity of the variables in our clinical prediction rule means that
14 the data collection required is feasible in busy medicine units.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 mortality⁵ and reduces the functional status of patients,⁶ as well as increasing the length of hospital stays⁷⁻⁸ 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 delirium²¹ 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).

1
2
3 The objective of this study was to derive and validate a simple clinical prediction
4 rule, based on variables that are easily measurable and are often routinely
5 taken on admission, to identify patients at high risk of developing delirium during
6 their hospital stay on an internal medicine ward.
7
8
9

10
11
12 The identification of these patients will allow us to introduce the necessary
13 preventative measures.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)

1
2
3 inattention, 3) disorganised thinking, and 4) altered level of consciousness. The
4
5 diagnosis of delirium required the presence of 1) and 2), and either 3) or 4) (or
6
7 both). This assessment was performed by two independent researchers, when
8
9 it was considered that patients were ready for discharge, after analysis of any
10
11 relevant data in their medical record and nursing report. Disagreements were
12
13 resolved by consensus with a third researcher. All these evaluators were
14
15 blinded to the potential predictive variables selected for the study.
16
17
18
19
20
21

22 *Potential predictors*

23
24
25 The potential predictive variables for delirium were selected after a systematic
26
27 review of the literature^{10-14 23-25}. We sought to identify variables that were easy
28
29 to measure and are often routinely recorded on admission to these wards.
30
31

32
33 The following variables were selected and measured on admission: age (years),
34
35 sex, systolic blood pressure (mmHg), heart rate (beats/min), respiratory rate
36
37 (breaths/minute), axillary temperature (°C), oxygen therapy (no: not used; and
38
39 yes: oxygen with nasal cannula, mask, and/or oxygen at home), fluid therapy,
40
41 presence of urinary catheter, level of consciousness (normal: alert; or altered:
42
43 drowsiness, unresponsiveness to voice, unresponsiveness to pain, and/or
44
45 generally unresponsive), diagnosis of infection at admission (respiratory, urinary
46
47 or other types of infections; or no infection: any other cause of admission),
48
49 admission in the previous year, admission in the previous month, hearing
50
51 impairment (use of a hearing aid, or deafness reported by the patient or
52
53 caregiver), vision impairment (regular use of glasses or reduction in visual
54
55 acuity reported by the patient or caregiver), and dementia (in a medical report or
56
57
58
59
60

1
2
3 reported by the caregiver). In addition, blood tests were taken on admission to
4
5 measure the following: haematocrit (%), levels of urea (mg/dl), creatinine
6
7 (mg/dl), sodium (mEq/l), potassium (mEq/l), and glucose (mg/dl), as well as
8
9 white blood cell ($10^3/\mu\text{l}$) and neutrophil ($10^3/\mu\text{l}$) counts. Lastly, certain
10
11 characteristics of patients prior to admission were also assessed: level of
12
13 dependence for activities of daily living (personal hygiene and grooming,
14
15 dressing and undressing, getting onto or off toilet, ambulation, bowel and
16
17 bladder control, and self-feeding) as dichotomous variables (dependent;
18
19 independent); presence of pressure ulcers, and excess alcohol intake (>60
20
21 g/ethanol/day), as well as use of certain types of medication: benzodiazepines,
22
23 antidepressants, antidementia drugs, antipsychotics, anti-Parkinson's drugs, or
24
25 anticonvulsants.
26
27
28
29
30
31
32

33 *Statistical analysis*

34
35
36 A descriptive analysis was carried out, based on the calculation of means and
37
38 standard deviations for continuous variables, and absolute or relative
39
40 frequencies as percentages for categorical variables. Subsequently, some
41
42 continuous variables were dichotomised using the median value.
43
44
45

46 *Sample size*

47
48
49 Assuming a prevalence of delirium at admission of 10%, it was calculated that
50
51 we needed 10 patients with delirium for each variable included in the model,
52
53 with the intention that the model should be as parsimonious as possible.
54
55
56
57
58
59
60

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

1
2
3 lowest risk category as the reference. The performance of the rule in the two
4
5 cohorts was explored using ROC curve analysis.
6
7

8 To assess the predictive~~diagnostic~~ accuracy of the rule, we constructed a 2x2
9
10 table for calculation of the following: sensitivity, specificity, and positive and
11
12 negative predictive values. The 95% confidence intervals of these indicators
13
14 were also calculated assuming a binomial distribution.
15
16

17
18 We used SPSS 19.0 and MedCalc for all the analysis.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Results

In the validation cohort, 13% of patients (52 out of 397) developed delirium, and in the derivation cohort the ~~incidence~~ 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, antimentia, or anticonvulsant drug contributing equally, while antipsychotic drugs were weighted by a factor of two. The

1
2
3 activities of daily living data were also dichotomised with a cut-off of reported
4
5 impairments in five activities.
6
7

8 The scores for the clinical prediction rule were assigned on the basis of
9
10 regression coefficients obtained in the logistic regression model (Table 7). One
11
12 point was given to patients older than 85 years, to those who had 2 or more
13
14 points in the variable drugs, and to those with impairments in five or more of the
15
16 activities of daily living considered. Therefore, the total score for the rule ranged
17
18 between 0 and 3.
19

20
21 The patients with delirium of the two cohorts scored similarly: 17% and 7%
22
23 scored 0, 48% and 30% scored ≤ 1 and 85% and 85% scored ≤ 2 in the
24
25 derivation and validation cohort respectively.
26
27

28
29 Table 9 and Figures 1 and 2 describe the performance of the rule in the
30
31 derivation and validation cohorts. In both cohorts, we observed higher rates of
32
33 delirium associated with higher scores on the rule, the model having a good
34
35 predictive power for the validation cohort (area under the ROC curve, AUC =
36
37 0.85). In contrast with what would be expected, the values obtained in the
38
39 validation cohort are better than those obtained in the derivation cohort, and this
40
41 is probably related to the higher incidence of delirium in validation group.
42
43

44
45 In particular, Table 9 lists the sensitivity (Se) and specificity (Sp), as well as the
46
47 positive and negative predictive values (PPVs and NPVs) obtained when the
48
49 rule was dichotomised as negative (a score of 0) or positive (as score of ≥ 1).
50
51 For the validation cohort, the Se, Sp, NPV, and PPV were 93.4%, 60.6%, 96%,
52
53 and 44% respectively
54
55
56
57
58
59
60

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 antimentia 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~~ 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 mentioned variables explain the almost two fold discrepancy in the incidence of delirium between the two cohorts.

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}

1
2
3 In the present study, we have only explored variables that are readily available
4 on admission, in order to use the predictive rule at that stage and be able to
5 introduce preventative measures immediately in high-risk patients. These would
6 include trying to avoid triggering factors for the development of delirium (such
7 as changes of room/ward, unnecessary catheterisation, inadequate oral
8 hydration, and polypharmacy).

9
10
11
12
13
14
15
16
17 Interestingly, the factors found to be good predictors for the development of
18 delirium in our study (age \geq 85, high level of dependence, and being on
19 psychotropic medication), to some extent, indirectly reflect the severity of the
20 organic brain damage in patients with delirium.

21
22
23
24
25
26
27 Another predictive rule for delirium in this type of patients has been published²¹
28 but showed a significantly lower performance than that we obtained (AUC =
29 0.66 [0.55-0.77] vs. AUC=0.85 [0.80-0.90] with our rule). Further, in our opinion,
30 it is also more difficult to apply than the rule we propose. The simplicity of the
31 variables included in our rule makes data collection a feasible task for busy
32 healthcare units.

33
34
35
36
37
38
39
40
41 Between 10% and 60% of patients admitted to hospital develop delirium,
42 depending on the type of patient, the ~~incidence~~ prevalence in frail elderly patients
43 being at the top of this range. In our study, it was 13% and 25% in the derivation
44 and validations cohorts, respectively. Delirium is well known to be difficult to
45 diagnose and a wide range of instruments have been developed to help detect
46 the condition.^{26 27} We used the Confusion Assessment Method²² that has a
47 sensitivity of 96% (95% CI 80-100%) and a specificity of 93% (95% CI 84-
48 100%). In our study, the doctors in charge of the diagnosis of delirium were
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 specialists in internal medicine, with considerable training and experience in the
4 management of this type of patients, any differences being resolved by
5 consensus with a third specialist. We note, however, that the diagnoses of
6 delirium were not confirmed by a psychiatrist. This may partially explain the low
7
8
9
10
11 ~~incidence~~ prevalence of delirium in our patients, that is, it may be that only the most
12 clinically striking cases, those which required pharmacological treatment, were
13 recognised.
14
15
16
17
18

19 The association between delirium and an increase of morbidity and mortality^{5 6 9}
20 is well known, as are the effectiveness of preventive measures to avoid the
21 development of the disease.¹⁵⁻¹⁸ The use of the proposed predictive rule would
22 allow us to classify around half of our inpatients (53%) as high-risk. Taking
23 preventative measures in this high risk group, up to 93.4% of those who
24 developed delirium in our study would have been covered by the measures and
25 might not have then developed the condition.
26
27
28
29
30
31
32
33
34

35 It would be interesting for the clinical predictive rule we propose to be validated
36 in other cohorts of frail elderly patients with worsening of multiple medical
37 conditions to check its external validity.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **ACKNOWLEDGEMENTS:** We would like to thank all the medical and nursing
4 staff of the Department of Internal Medicine at Donostia University Hospital for
5 their contribution to the study.
6
7
8

9
10 **CONTRIBUTORS:** JM, AB, JIE and IU participated in the design of the study.
11 JM, AB, IB, XG, CA and NL collected all data. JIE and IU carried out the
12 statistical analysis. JM, IU and JIE drafted the manuscript. All authors approved
13 the final version to be published. IU and JM are the guarantors.
14
15
16

17
18 **COMPETING INTERESTS:** All authors have completed the Unified Competing
19 interests form at http://www.icmje.org/coi_disclosure.pdf (available on request
20 from the corresponding author) and declare: no support from any organisation
21 for the submitted work; no financial relationships with any organisations that
22 might have an interest in the submitted work in the previous three years; and no
23 other relationships or activities that could appear to have influenced the
24 submitted work.
25
26
27
28
29
30
31
32
33
34

35 **ETHICAL APPROVAL:** The design was evaluated and then approved by the
36 Clinical Research Ethics Committee of the Gipuzkoa Health region.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES:

- 1) Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing*. 2009; 38: 19-26
- 2) Trzepacz PT. Delirium. Advances in diagnosis, pathophysiology, and treatment. *Psychiatric Clinics of North America* 1996; 19 (3): 429-448.
- 3) Leentjens AF, van der Mast RC. Delirium in elderly people: an update. *Curr Opin Psychiatry*. 2005 May; 18 (3): 325-330.
- 4) Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010; 304: 443-451.
- 5) McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Archives of Internal Medicine* 2002; 162 (4): 457-463.
- 6) Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. *International Study of Post-Operative Cognitive Dysfunction*. *Lancet* 1998; 351 (9106): 857-861.
- 7) McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? *Journal of the American Geriatrics Society* 2003 51 (11):1539-1546.

1
2
3
4
5
6 8) Stevens LE, de Moore GM, Simpson JM. Delirium in hospital: does it
7 increase length of stay? Australian & New Zealand Journal of Psychiatry 1998;
8 32 (6): 805-808.
9

10
11
12
13
14 9) Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium
15 contribute to poor hospital outcomes? A three-site epidemiologic study. Journal
16 of General Internal Medicine 1998; 13: 234-242.
17
18

19
20
21
22
23 10) Inouye SK. Delirium in hospitalized older patients: recognition and risk
24 factors. Journal of Geriatric Psychiatry & Neurology 1998; 11 (3): 118-125;
25 discussion 157-158.
26
27

28
29
30 11) Fick DM; Agostini JV; Inouye SK. Delirium superimposed on dementia: a
31 systematic review. J Am Geriatr Soc 2002; 50 (10):1723-1732.
32
33

34
35 12) Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized
36 elderly persons. Predictive model and interrelationship with baseline
37 vulnerability. JAMA. 1996; 275 (11): 852-857.
38
39

40
41
42
43 13) Laurila JV, Laakkonen ML, Tilvis RS, Pitkala KH. Predisposing and
44 precipitating factors for delirium in a frail geriatric population. J Psychosom
45 Res. 2008 Sep; 65 (3): 249-254.
46
47

48
49
50 14) Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S,
51 Bossaert L. Risk factors for intensive care delirium: a systematic review.
52 Intensive Crit Care Nurs. 2008 Apr; 24 (2):98-107.
53
54

- 1
2
3 15) Inouye, S, Bogardus, ST, Charpentier, PA, et al. A multicomponent
4 intervention to prevent delirium in hospitalized older patients. *N Engl J Med*
5 1999; 340: 669-676.
6
7
8
9
10 16) Milisen K, Lemiengre J, Braes T, Foreman M D. Multicomponent
11 intervention strategies for managing delirium in hospitalized older people:
12 systematic review. *Journal of Advanced Nursing* 2005; 52 (1): 79-90
13
14
15
16
17
18 17) Vidan MT, Sanchez E, Alonso M, Montero B, Ortiz J, Serra JA. An
19 Intervention Integrated into Daily Clinical Practice Reduces the Incidence of
20 Delirium During Hospitalization in Elderly Patients. *J Am Geriatr Soc* 2009;
21 57:2029–2036.
22
23
24
25
26 18) Siddiqi N, Holt R, Britton AM, Holmes J. Interventions for preventing
27 delirium in hospitalised patients. *Cochrane Database of Systematic Reviews*
28 2007, Issue 2. Art. No.: CD005563. DOI: 10.1002/14651858.CD005563.pub2.
29
30
31
32
33 19) Leslie DL, Marcantonio ER, Zhang Y, Summer LLs, Intuye SK. One-Year
34 Health Care Costs Associated With Delirium in the Elderly Population. *Arch*
35 *Intern Med.* 2008;168 (1):27-32
36
37
38
39 20) Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and
40 suggested modifications of methodological standards. *JAMA.* 1997 Feb 12; 277
41 (6):488-494.
42
43
44
45
46
47
48 21) Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model
49 for delirium in hospitalized elderly medical patients based on admission
50 characteristics. *Ann Intern Med.* 1993 Sep 15; 119 (6): 474-481.
51
52
53
54
55
56
57
58
59
60

1
2
3 22) Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI.
4 Clarifying confusion: the confusion assessment method. A new method for
5 detection of delirium. *Ann Intern Med.* 1990 Dec 15;113 (12):941-948.
6
7
8

9
10
11 23) Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly
12 hospitalized patients. *J Gen Intern Med.* 1998 Mar; 13 (3):204-212.
13
14

15
16 24) Pisani, MA, Murphy, TE, Van Ness, PH, et al. Characteristics associated
17 with delirium in older patients in a medical intensive care unit. *Arch Intern Med*
18 2007; 167:1629-1634.
19
20
21

22
23 25) McCusker, J, Cole, M, Abrahamowicz, M, et al. Environmental risk factors
24 for delirium in hospitalized older people. *J Am Geriatr Soc* 2001; 49:1327-1334.
25
26
27

28
29 26) Camilla L. Wong, MD, Jayna Holroyd-Leduc, MD, FRCPC, David L. Simel,
30 MD, MHS, Sharon E. Straus, MD, MSc, FRCPC. Does This Patient Have
31 Delirium? Value of Bedside Instruments. *JAMA.* 2010; 304 (7): 779-786
32
33
34
35

36
37 27) Moraga AV, Rodriguez-Pascual C. Acurate diagnosis of delirium in elderly
38 patients. *Curr Opin Psychiatry.* 2007 May; 20 (3):262-267.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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/ μ l)	12.1 (12.2)	10.1(4.7)	N.S
Neutrophils (10e3/ μ l)	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

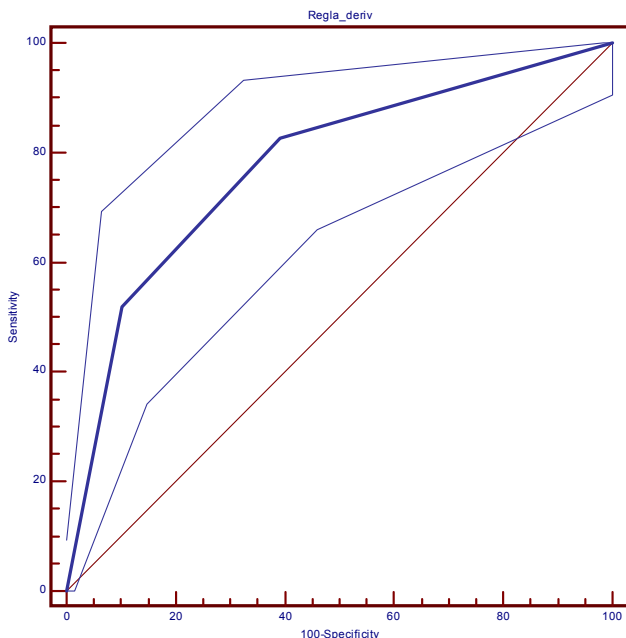
Specificity = 60.6%, 95% CI 54.1 to 66.8

PPV = 44.4%, 95% CI 36.9 to 52.1

NPV = 96.5%, 95% CI 92 to 98.5

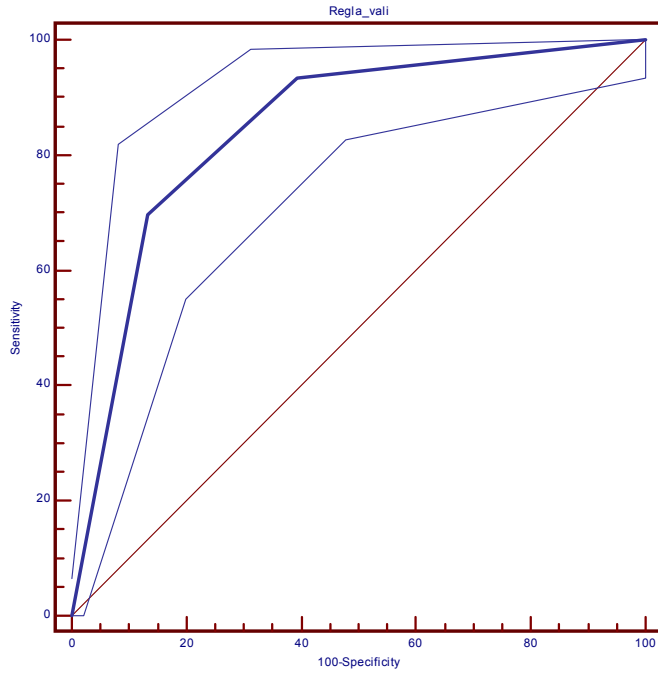
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: ROC curve for the derivation cohort



er review only

Figure 2: ROC curve for the validation cohort



review only

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>.