BMJ Open

Validation of an automated delirium prediction model (DEMO Delirium Model): an observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016654
Article Type:	Research
Date Submitted by the Author:	10-Mar-2017
Complete List of Authors:	Mestres Gonzalvo, Carlota; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology de Wit, Hugo; Zuyderland Medisch Centrum Heerlen, Clinical Pharmacy, Pharmacology and Toxicology van Oijen, Brigit; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Debben, Debbie; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Hurkens, Kim; Zuyderland Medisch Centrum Heerlen, Geriatric Medicine, Department of Internal Medicine Mulder, Wubbo; Maastricht Universitair Medisch Centrum+, Internal Medicine Janknegt, Rob; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Schols, Jos; Maastricht University, Department of General Practice, School for Public Health and Primary Care (CAPHRI) Verhey, Frans; Maastricht University Faculty of Health Medicine and Life Sciences, Psychiatry and Neuropsychology, Alzheimer Centrum Limburg / School for Mental Health and Neurosciences Winkens, Bjorn; Maastricht University, van der Kuy, Paul-Hugo; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Mental health
Keywords:	GERIATRIC MEDICINE, Delirium & cognitive disorders < PSYCHIATRY, PSYCHIATRY

Validation of an automated delirium prediction model (DEMO Delirium Model):
an observational study

C Mestres Gonzalvo (hospital pharmacist in training)[1], HAJM de Wit (hospital pharmacist)[1], BPC van Oijen (hospital pharmacist)[1], D Deben (hospital pharmacist in training)[1], KPGM Hurkens (internist geriatrician)[2], WJ Mulder (internist geriatrician)[3], R Janknegt (hospital pharmacist)[1], JMGA Schols (Professor of Old Age Medicine)[4], FR Verhey (Professor of Geriatric Psychiatry)[5], B Winkens (statistician)[6], PHM van der Kuy (hospital pharmacist)[1]

[1]Department of Clinical Pharmacy, Pharmacology and Toxicology, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen and Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands.
[2]Section of Geriatric Medicine, Department of Internal Medicine, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen and Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands.
[3]Department of Internal Medicine, Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands.
[4]Department of Family Medicine and Department of Health Services Research, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[5]Department of Psychiatry and Neuropsychology, Alzheimer Centrum Limburg/School for Mental Health and Neurosciences, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[6]Department of Methodology and Statistics, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyeplein 1, 6229 HA Maastricht, The Netherlands.

Submitting and corresponding author:
Carlota Mestres Gonzalvo
Department of Clinical Pharmacy, Pharmacology and Toxicology
Zuyderland Medical Centre
Dr H van der Hoffplein 1
6162 BG Sittard-Geleen
Phone: +31-88-4597708
E-mail: c.mestresgonzalvo@zuyderland.nl

ABSTRACT

Objectives: Delirium is an under-diagnosed, severe, and costly disorder. In 30-40% of the cases it can be prevented. A fully automated model to predict delirium (DEMO) in older people was retrospectively developed, but has not yet been validated; the objective of this study is to prospectively validate DEMO in the hospital setting.

Setting: Secondary care, one hospital with two locations

Design: Observational study

Participants: 383 randomly selected patients over 60 years admitted to Zuyderland were included. Patients who presented with a delirium on admission were excluded.

Primary outcome measures: sensitivity and specificity of DEMO

Results: A total of 383 patients was included in this study. The analysis was performed 1, 3 and 5 days after DEMO-score. Sensitivity was 87.9% (CI: 0.709 to 0.960), 90.9% (CI: 0.774 to 0.971), and 92.0% (0.799 to 0.974) for 1, 3, and 5 days after DEMO-score respectively. Specificity was 72.6% (0.675 to 0.771), 74.9% (0.699 to 0.794) and 76.3% (0.713 to 0.807) for 1, 3, and 5 days after DEMO-score respectively.

Conclusion: DEMO is a satisfactory prediction model. The next step is to apply the DEMO in clinical practice so that physicians are alerted when a patient is at increased risk of developing delirium and can implement prevention measures.

Strengths and limitations of this study

- A delirium can be electronically predicted using the DEMO (Delirium MOdel) with reasonably good sensitivity and specificity.
- DEMO can be applied into clinical practice facilitating earlier recognition and diagnosis of delirium.
- Important factors that could predict a delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because they were not electronically available.

INTRODUCTION

A delirium or acute confusional state is a transient attention and cognition disorder that develops over a short period of time, occurring mainly in hospitalised patients and people aged 60 years and over. Delirium is an under-diagnosed, severe (increased mortality), costly and often preventable disorder [1-3]. Its severity and symptoms can range considerably but the main features are impaired cognitive and sensory functions, reduced consciousness and diminished attention; in addition it is often accompanied by problems in psychomotor activity, the circadian rhythm and emotions.

The prevalence and incidence of delirium in the general population vary widely depending on the setting. The overall prevalence in the community is estimated at 1-2%. In the hospital setting this increases to between 10-31% at hospital admission and 3-29% during hospitalisation. The incidence increases up to 87% when considering more specialised populations such as elderly, postoperative, intensive care and/or palliative care [4-11]. In 30-40% of cases delirium is preventable, which in combination with its associated high costs (ranging from US$164 billion to US$182 billion per year) makes it a perfect target for interventions by healthcare professionals [1, 4, 13-15]. As a result, a great number of screening tools have been developed and are widely used to detect early onset delirium which in turn can allow treatment measures to be introduced in a timelier manner [16-21]. These tools support health care professionals to establish and quantify symptoms associated with delirium [19-23]. Once the diagnosis has been established the underlying medical condition can be targeted and delirium managed appropriately.

Treatment measures for delirium include pharmacological and non-pharmacological symptom-targeted measures. Haloperidol or atypical anti-psychotics are the standard pharmacological treatment for delirium, while non-pharmacological measures comprise environmental interventions such as emphasising orientation, mobilisation, vision/hearing optimisation, and sleep enhancement [1, 4, 24-27]. There are several approaches to prevent a delirium. It is known that non-pharmacological measures are effective in preventing delirium. There are also indications that prophylactic haloperidol might be effective. However, study results regarding the value of haloperidol as an adjunct to non-pharmacological approaches are controversial [25-34]. Different models have been developed for the detection of delirium, both for intensive care patients and hospitalised older people. These models use different factors to calculate an individual's risk of developing delirium, such as predictive variables (infection, certain drugs) and predisposing factors (cognitive impairment, previous delirium or the reason for hospital admission). These models are often based on a manual calculation of the individual risk of delirium [35-38].

Screening instrument

A fully automated model to predict delirium in older people (over 60 years) was developed in 2013 at Zuyderland Medical Centre. This DElirium MOdel (DEMO) uses only electronically available data to predict the occurrence of delirium. The used predictive variables were age, polypharmacy, use of anti-

dementia drugs, antidepressants, anti-Parkinson's agents, anti-diabetic drugs, analgesia and / or sleeping tablets. This model can be applied hospital wide and has an "Area under Receiver Operating Characteristic" (AUROC: measure for model prediction quality) of 0.770 (95% CI 0736-0804) with a sensitivity of 78.2% and a specificity of 63.7%, if 14.1% is used as a cut-off value for the predicted probability of developing delirium. The DEMO was retrospectively developed, but has not yet been validated [4].

Therefore, the objective of this study is to validate DEMO in the hospital setting. In order to do so the accuracy (main study parameter) of DEMO, i.e. sensitivity (proportion of delirium patients who test positive) and specificity (proportion of non-delirium patients who test negative) will be calculated. In addition to these parameters, the positive and negative likelihood ratios with their 95% CI will be computed.

METHODS

This is an observational study into the ability of DEMO to predict a delirium in an elderly hospital population. It was conducted in Zuyderland Medical Center (locations Sittard and Heerlen) in the period January 2016 to October 2016. The medical ethics committee approved this study.

Patients over 60 years admitted to Zuyderland were selected for enrollment. Patients who presented with a delirium on admission were excluded.

In our study wherein the DEMO was developed, an incidence rate of 17.4% was used [4]. Assuming the same sensitivity of 0.75 (75%), we calculated that 33 delirium patients were needed in order to ensure that the width of the corresponding 95% confidence interval is not greater than 0.30. Regarding the specificity, the number of non-delirium patients will be much larger, and hence the width of the 95% confidence interval (CI) for specificity will be much smaller than 0.30.

It was calculated that at least 332 patients were needed to identify 33 delirium patients. To be sure, taking into account exclusion criteria or a smaller percentage of patients who developed delirium, enough patients were screened to achieve the 33 delirium patients (i.e. 383 patients).

The DEMO analyses daily all hospitalised patients ≥ 60 years old in the different wards and predicts whether a patient is at risk of developing a delirium in the 24hours post analysis. The EPR (Electronic Patient Record) was accessed at a later date to confirm if the patient had developed delirium.

To validate the DEMO patients were randomly selected (using https://www.randomlists.com/team-generator). An extraction from the EPR of these patients was made between 31-12-2015 and 31-10-2016.

A search in the EPR was performed per patient and date using the following search terms: "delirium", "delirious". Afterwards this search was compared with the risk score from the DEMO to evaluate whether the prediction was good (risk ≥ 14.1%), which means that the diagnosis (search terms) was used as a reference to test the DEMO's screening characteristics. In this way, they were classified as True Positive (TP), True Negative (TN), False Positive (FP), False Negative (FN).
This evaluation was performed on different SETS in order to evaluate the predictive value of the DEMO as it was developed (delirium within 24 hours), and to investigate whether other SETS would give better results:

SET 1: "delirium" or "delirious" as diagnosis within 1 day after the DEMO analysis.
SET 2: "delirium" or "delirious" as diagnosis within 3 days after the DEMO analysis.
SET 3: "delirium" or "delirious" as diagnosis within 5 days after the DEMO analysis.

If the results of the diagnostic test (TP / TN / FP / FN) could not be established for a patient as a result of unclear data, this patient was excluded from the analysis (e.g. DD delirium, delirium? Patient seems confused, etc.). During the study physicians were blinded to DEMO scores to avoid bias. The sensitivity, specificity and likelihood ratios with corresponding 95% confidence intervals were calculated using an online calculator (http://vassarstats.net/clin1.html).

The differences in age and gender between delirium and non-delirium groups were tested using the independent samples t-test and chi-square test, respectively. IBM SPSS statistics for Windows (version 23.0) was used to perform these tests. A two-sided p-value smaller than or equal to 0.05 was considered statistically significant.

RESULTS

The study lasted eight months. A total of 383 patients were included in this study.
Each set was independently analyzed. The results of the diagnostic test (TP/FP/FN/TN) for SETS 1-3 are shown in Table 1. The analysis for all 3 sets including prevalence estimates, sensitivity, specificity, and likelihood ratios are presented in Table 2.

SET 1, SET 2 and SET 3 showed an increasing sensitivity and specificity

Taking into account what we considered as clinically relevant, SET 3 was the most advantageous as the number of FN remained relatively small and the number of FP decreased in comparison to SET 1 and SET 2. In other words, we choose a higher sensitivity over a higher specificity given the consequences of missing a potential delirium compared to the consequences of falsely predicting a delirium. In the case of falsely predicting a delirium, non-pharmacological measures would be applied, meaning unnecessary attention is given to these patients.

The baseline characteristics for SET 3 (age and gender) are shown in Table 3.

Table 3. Baseline characteristics SET 3

	Delirium (n = 50)	Non-delirium (n = 333)	Total (n = 383)
Mean age (SD)	84.7 (8.1) *	74.1 (9.1) *	75.5 (9.6)
Man	26 (52.0%)	168 (50.5%)	194 (50.7%)
Woman	24 (48.0%)	165 (49.5%)	189 (49.3%)

* Statistically significant

A statistically significant difference was found in mean age between delirium and non-delirium patients (equal variances assumed, p <0.001, mean difference = 10.6, 95%CI 7.9 to 13.3). There was no significant difference in percentage of delirium between men and women (p = 0.176).

DISCUSSION AND CONCLUSION

In the current study a previously developed model for predicting delirium has been prospectively validated. Based on the current data and the high sensitivity and specificity it can be concluded that the DEMO is clinically applicable.

We found sensitivity and specificity rates that were higher than reported in the study of de Wit et al., which may be due to the fact that that study had only checked the patients' medical history for delirium but not the entire EPR. Moreover, de Wit et al. had performed the search only on the word "delirium" and in the current study "delirium" and "delirious" were used. Furthermore, in the current study, in such circumstances that a delirium is unclear these patients were excluded, whereas such patients were included in the development of the delirium model [4].

The present study has some limitations. First of all, the validation of the DElirium MOdel depends on how and when a physician reports that a patient has developed a delirium. Furthermore, the number of delirium patients may still be rather low; although for SETS 2-3 is higher than originally planned.

The DEMO used exclusively electronically available data. Important factors that could predict a delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because they were not electronically available. By making this data electronically available, the prediction quality of DEMO could be improved 22, 23, 25, 34]. Taking into account that the registration of such factors is becoming increasingly important and mandatory, it is only a matter of time until such important factors can be used in the DEMO [2,3].

DElirum MOdel is a fully automated satisfactory prediction model. The next step is to apply the DEMO in clinical practice so that physicians are alerted when a patient is at increased risk of developing delirium and can implement prevention measures, non-pharmacological and/or pharmacological. This will facilitate earlier recognition and diagnosis.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from ABC Company for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

FUNDING

This work was supported by ZonMw (the Netherlands Organisation for Health Research and Development) grant number [113101001]

AUTHORS' CONTRIBUTIONS

All authors have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; They all have been involved in drafting the manuscript and revising it critically for important intellectual content; They all have given final approval of the version to be published; and they all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conception or design of the work

C Mestres Gonzalvo
HAJM de Wit
BPC van Oijen
DS Deben
KPGM Hurkens
WJ Mulder
R Janknegt
JMGA Schols
FR Verhey
B Winkens
PHM van der Kuy

Data collection

C Mestres Gonzalvo
DS Deben

Data analysis and interpretation

C Mestres Gonzalvo
FR Verhey
B Winkens
PHM van der Kuy

Drafting the article

C Mestres Gonzalvo

Critical revision of the article

HAJM de Wit

BPC van Oijen

JMGA Schols

FR Verhey

B Winkens

PHM van der Kuy

Final approval of the version to be published

C Mestres Gonzalvo

HAJM de Wit

BPC van Oijen

DS Deben

KPGM Hurkens

WJ Mulder

R Janknegt

JMGA Schols

FR Verhey

B Winkens

PHM van der Kuy

TRANSPARENCY DECLARATION

C. Mestres Gonzalvo affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING

All data is anonymized and will be confidentially handled. Only the investigators have access to the data.

All patient data will be kept for as long as the project is being conducted.

EXCLUSIVE LICENCE

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the publishers.

(http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.doc)

REFERENCES

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-22.
2. Delirium: Diagnosis, prevention and management. NICE guidelines [CG103] Published date: July 2010
3. Delirium for adults Dutch guideline. Richtlijn Delier Volwassenen. Nederlandse Vereniging voor Klinische Geriatrie (NVKG) 2013
4. Hugo AJM de Wit, Bjorn Winkens, Carlota Mestres Gonzalvo, Kim PGM Hurkens, Wubbo J Mulder, Rob Janknegt, Frans R Verhey, Paul-Hugo M van der Kuy, and Jos MGA Schols. The development of an automated ward independent delirium risk prediction model Int J Clin Pharm (2016) 38:915–923
5. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35(4):350-64.
6. Ryan DJ, O'Regan NA, Caoimh RÓ, et al: Delirium in an adult acute hospital population: predictors, prevalence and detection. BMJ Open 2013; 3(1). http://dx.doi.org/10.1136/bmjopen-2012-001772
7. Inouye SK. Delirium in hospitalized older patients. Clin. Geriatr. Med. 1998;14:745–764.
8. Bruce, A. J., Ritchie, C. W., Blizard, R., Lai, R. & Raven, P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. Int. Psychogeriatr. 19, 197-214 (2007).
9. Girard, T. D. & Ely, E. W. Delirium in the critically ill patient. Handb. Clin. Neurol. 90, 39-56 (2008)
10. Inouye SK. Delirium in older persons. N. Engl. J. Med. 2006;354:1157–1165
11. Pisani, M. A., McNicoll, L. & Inouye, S. K. Cognitive impairment in the intensive care unit. N. Engl. J. Med. 24, 727-737 (2003)
12. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008 Jan 14;168(1):27-32. PubMed PMID: 18195192.
13. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
14. WHO Regional Offi ce for Europe. European hospital morbidity database. Copenhagen: World Health Organization, 2012.
15. Organisation for Economic Co-operation and Development. OECD health data 2012. Paris: Organisation for Economic Co-operation and Development, 2012.
16. Adamis D, Sharma N, Whelan PJ, Macdonald AJ. Delirium scales: a review of current evidence. Aging Ment Health 2010; 14: 543–55.
17. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA 2010; 304: 779–86.
18. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec 15;113(12):941-8. PubMed PMID: 2240918. Epub 1990/12/15.
19. Jin H. Han MD, MSc1,and Eduard E. Vasilevskis. Ultrabrief delirium assessments—are they ready for primetime? DOI: 10.1002/jhm.2478

20. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pract. 2003 Spring;17(1):31-50. PubMed PMID: 12751884. Epub 2003/05/20.
21. van Velthuijsen EL, et al. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. Int J Geriatr Psychiatry. 2016 Sep;31(9):974-89. doi: 10.1002/gps.4441. Epub 2016 Feb 21.
22. 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):249-54. PubMed PMID: 18707947. Epub 2008/08/19.
23. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord. 1999 Sep-Oct;10(5):393-400. PubMed PMID: 10473946. Epub 1999/09/04.
24. Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. Neurotherapeutics. 2012 Jan;9(1):158-75. doi: 10.1007/s13311-011-0102-9.
25. Young J, Leentjens AF, George J, Olofsson B, Gustafson Y. Systematic approaches to the prevention and management of patients with delirium. J Psychosom Res. 2008 Sep;65(3):267-72. PubMed PMID: 18707950.
26. Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. Psychosomatics. 2013 Mar-Apr;54(2):124-31. PubMed PMID: 23380670.
27. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005 Oct;53(10):1658-66. PubMed PMID: 16181163.
28. Wang W1, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, Chen KS, Gu XE, Zhu SN. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. Crit Care Med. 2012 Mar;40(3):731-9. doi: 10.1097/CCM.0b013e3182376e4f.
29. Anne JH Vochteloo, Sophie Moerman, Boudewijn LS Borger van der Burg, Maarten de Boo, Mark R de Vries, Dieu-Donné Niesten, Wim E Tuinebreijer, Rob GHH Nelissen and Peter Pilot. Delirium risk screening and haloperidol prophylaxis program in hip fracture patients is a helpful tool in identifying high-risk patients, but does not reduce the incidence of delirium. BMC Geriatrics 2011, 11:39 doi:10.1186/1471-2318-11-39
30. Schrader SL, Wellik KE, Demaerschalk BM, Caselli RJ, Woodruff BK, Wingerchuk DM. Adjunctive haloperidol prophylaxis reduces postoperative delirium severity and duration in at-risk elderly patients. Neurologist 2008;14:134-7.
31. van den Boogaard M, Schoonhoven L, van Achterberg T, et al: Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Crit Care 2013; 17:R9
32. E.J.M. Schrijver et al. Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: A systematic review of current evidence. European Journal of Internal Medicine 27 (2016) 14–23

33. Hshieh et al. JAMA Intern Med. 2015;175(4):512-520. doi:10.1001/jamainternmed.2014.7779
34. Kishi T, et al. J Neurol Neurosurg Psychiatry 2016;87:767–774. doi:10.1136/jnnp-2015-311049

35. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012;344:e420. PubMed PMID: 22323509. Pubmed Central PMCID: 3276486.
36. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med. 1993 Sep 15;119(6):474-81. PubMed PMID: 8357112.
37. Carrasco MP, Villarroel L, Andrade M, et al. Development and validation of a delirium predictive score in older people. Age Ageing. 2014;43(3):346-51.
38. Douglas VC, Hessler CS, Dhaliwal G, et al. The AWOL tool: derivation and validation of a delirium prediction rule. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2013;8(9):493-9.)

Table 1. Cross-table of the predicted test result of the prediction model (DEMO positive or negative) and diagnosis (delirium positive or negative) for SET 1, SET 2, and SET 3.

	SET 1		SET 2		SET 3	
	Delirium positive	Delirium negative	Delirium positive	Delirium negative	Delirium positive	Delirium negative
DEMO Positive	29	96	40	85	46	79
DEMO Negative	4	254	4	254	4	254

Table 2. Estimates of the prevalence, sensitivity, specificity, and likelihood ratios with corresponding 95% confidence intervals for SET 1, SET 2, and SET 3.

	SET 1			**SET 2**			**SET 3**		
	Estimated value	95% confidence interval		Estimated value	95% confidence interval		Estimated value	95% confidence interval	
		Lower limit	Upper limit		Lower limit	Upper limit		Lower limit	Upper limit
Prevalence	0.086 (8.6%)	0.061	0.120	0.115 (11.5%)	0.086	0.152	0.131 (13.1%)	0.099	0.169
Sensitivity	0.879 (87.9%)	0.709	0.960	0.909 (90.9%)	0.774	0.971	0.920 (92.0%)	0.799	0.974
Specificity	0.726 (72.6%)	0.675	0.771	0.749 (74.9%)	0.699	0.794	0.763 (76.3%)	0.713	0.807
Positive likelihood ratio	3.204	2.59	3.962	3.626	2.950	4.457	3.878	3.146	4.780
Negative likelihood ratio	0.167	0.067	0.419	0.121	0.048	0.310	0.105	0.041	0.269

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5	
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	4-5	
Bias	9	Describe any efforts to address potential sources of bias	-	
Study size	10	Explain how the study size was arrived at	4	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	Table 2
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	5-6
		(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	Table 3
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2
		(*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	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
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	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-7
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
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	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Validation of an automated delirium prediction model (DEMO Delirium Model): an observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016654.R1
Article Type:	Research
Date Submitted by the Author:	15-May-2017
Complete List of Authors:	Mestres Gonzalvo, Carlota; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology de Wit, Hugo; Zuyderland Medisch Centrum Heerlen, Clinical Pharmacy, Pharmacology and Toxicology van Oijen, Brigit; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Debben, Debbie; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Hurkens, Kim; Zuyderland Medisch Centrum Heerlen, Geriatric Medicine, Department of Internal Medicine Mulder, Wubbo; Maastricht Universitair Medisch Centrum+, Internal Medicine Janknegt, Rob; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Schols, Jos; Maastricht University, Department of General Practice, School for Public Health and Primary Care (CAPHRI) Verhey, Frans; Maastricht University Faculty of Health Medicine and Life Sciences, Psychiatry and Neuropsychology, Alzheimer Centrum Limburg / School for Mental Health and Neurosciences Winkens, Bjorn; Maastricht University, van der Kuy, Hugo; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Mental health
Keywords:	GERIATRIC MEDICINE, Delirium & cognitive disorders < PSYCHIATRY, PSYCHIATRY

Validation of an automated delirium prediction model (DEMO Delirium Model):
an observational study

C Mestres Gonzalvo (hospital pharmacist in training)[1], HAJM de Wit (hospital pharmacist)[1], BPC van Oijen (hospital pharmacist)[1], D Deben (hospital pharmacist in training)[1], KPGM Hurkens (internist geriatrician)[2], WJ Mulder (internist geriatrician)[3], R Janknegt (hospital pharmacist)[1], JMGA Schols (Professor of Old Age Medicine)[4], FR Verhey (Professor of Geriatric Psychiatry)[5], B Winkens (statistician)[6], PHM van der Kuy (hospital pharmacist)[1]

[1]Department of Clinical Pharmacy, Pharmacology and Toxicology, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen and Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands.
[2]Section of Geriatric Medicine, Department of Internal Medicine, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen and Henri Dunantstraat 5, 6419 PC Heerlen, The Netherlands.
[3]Department of Internal Medicine, Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands.
[4]Department of Family Medicine and Department of Health Services Research, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[5]Department of Psychiatry and Neuropsychology, Alzheimer Centrum Limburg/School for Mental Health and Neurosciences, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[6]Department of Methodology and Statistics, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyeplein 1, 6229 HA Maastricht, The Netherlands.

Submitting and corresponding author:
Carlota Mestres Gonzalvo
Department of Clinical Pharmacy, Pharmacology and Toxicology
Zuyderland Medical Centre
Dr H van der Hoffplein 1
6162 BG Sittard-Geleen
Phone: +31-88-4597708
E-mail: c.mestresgonzalvo@zuyderland.nl

ABSTRACT

Objectives: Delirium is an under-diagnosed, severe, and costly disorder which in 30-40% of the cases can be prevented. A fully automated model to predict delirium (DEMO) in older people has been developed and the objective of this study is to validate the model in a hospital setting.

Setting: Secondary care, one hospital with two locations

Design: Observational study

Participants: The study included 450 randomly selected patients over 60 years of age admitted to Zuyderland Medical Centre. Patients who presented with a delirium upon admission were excluded.

Primary outcome measures: Development of delirium by chart review.

Results: A total of 383 patients were included in this study. The analysis was performed 1, 3 and 5 days after DEMO-score. Sensitivity was 87.9% (CI: 0.709 to 0.960), 90.9% (CI: 0.774 to 0.971), and 92.0% (0.799 to 0.974) for 1, 3, and 5 days after DEMO-score, respectively. Specificity was 72.6% (0.675 to 0.771), 74.9% (0.699 to 0.794) and 76.3% (0.713 to 0.807) for 1, 3, and 5 days after DEMO-score, respectively.

Conclusion: DEMO is a satisfactory prediction model. The next step will be to validate the DEMO in a cohort where the outcome of delirium is assessed prospectively in person by the physician, and the DEMO model is used for retrospective measurements. In the future DEMO will be applied in clinical practice so that physicians will be alerted when a patient is at an increased risk of developing delirium, which will facilitate earlier recognition and diagnosis, and thus will allow the implementation of prevention measures, both non-pharmacological and/or pharmacological.

Strengths and limitations of this study

- A delirium can be predicted electronically by using DEMO (Delirium MOdel) with reasonably good sensitivity and specificity.
- DEMO can be applied into clinical practice to facilitate earlier recognition and diagnosis of delirium.
- Important factors that could predict a delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because this data is not yet electronically available.

INTRODUCTION

A delirium or acute confusional state is a transient attention and cognition disorder that develops over a short period of time and occurs mainly in hospitalised patients and people aged 60 years and over. Delirium is an under-diagnosed, severe (increased mortality), costly and often preventable disorder [1-3]. Its severity and symptoms can range considerably but the main features are impaired cognitive and sensory functions, reduced consciousness, and diminished attention; in addition, it is often accompanied by problems in psychomotor activity, the circadian rhythm, and emotions.

The prevalence and incidence of delirium in the general population differ widely depending on the setting. The overall prevalence in the community is estimated at 1-2%. In a hospital setting, this increases to between 10-31% at the time of hospital admission and 3-29% during hospitalisation. The incidence increases up to 87% when more specialised populations such as the elderly and people in postoperative, intensive care and/or palliative care are considered [4-11]. In 30-40% of the cases, delirium is preventable, which in combination with its associated high costs (ranging from US$164 billion to US$182 billion per year) makes it a perfect target for interventions by healthcare professionals [1, 4, 12-15]. As a result, a great number of screening tools have been developed and are widely used to detect early onset of delirium which in turn can allow treatment measures to be introduced in a timely manner [16-21]. These tools help health care professionals to establish and quantify symptoms associated with delirium [19-23]. Once the diagnosis has been established, the underlying medical condition can be targeted and delirium managed appropriately.

Treatment measures for delirium include both pharmacological and non-pharmacological symptom-targeted measures. There is no universally accepted treatment for delirium after it has developed [24]. Though commonly used, there is little evidence that supports the use of antipsychotics in the treatment of delirium [25, 26].

The need for DEMO becomes more compelling in the absence of an effective delirium treatment: preventing delirium is more effective than treating delirium after it has occurred. There are several approaches to prevent a delirium. It is known that non-pharmacological measures are effective in preventing delirium. Such measures comprise environmental interventions such as emphasising orientation, mobilisation, vision/hearing optimisation, and sleep enhancement [1, 4, 27-30]. There are also indications that prophylactic haloperidol might be effective. However, study results regarding the value of haloperidol as an adjunct to non-pharmacological approaches are controversial [28-37] and a recent meta-analysis by Neufeld et al. concludes that there is no evidence to support pharmacologic treatment for prevention of delirium [35]. Different models have been developed for the detection of delirium, both for intensive care patients and hospitalised older people. These models use different factors to calculate an individual's risk of developing delirium, such as predictive variables (infection, certain drugs) and predisposing factors (cognitive impairment, previous delirium or the reason for hospital admission). These models are often based on a manual evaluation of the individual risk of delirium [38-42].

Screening instrument

A fully automated model to predict delirium in older people (over 60 years) was developed in 2013 at Zuyderland Medical Centre. This DElirium MOdel (DEMO) uses only electronically available data to predict the occurrence of delirium. The used predictive variables were: age, polypharmacy, use of anti-dementia drugs, antidepressants, anti-Parkinson's agents, anti-diabetic drugs, analgesia and/or sleeping tablets. This model can be applied hospital-wide and has an "Area under Receiver Operating Characteristic" (AUROC: measure for model prediction quality) of 0.770 (95% CI 0736-0804) with a sensitivity of 78.2% and a specificity of 63.7%, when 14.1% is used as a cut-off value for the predicted probability of developing delirium. The DEMO model was developed retrospectively but has not yet been validated [4]. Table 2 (supplementary tables).

Therefore, the objective of this study is to validate DEMO in the hospital setting. In order to do so the system's accuracy (main study parameter), i.e. sensitivity (proportion of delirium patients who test positive) and specificity (proportion of non-delirium patients who test negative), will be calculated. In addition to these parameters, the positive and negative likelihood ratios with their 95% CI will be computed.

METHOD

This is an observational study into the ability of DEMO to predict a delirium in an elderly hospital population. It was conducted in Zuyderland Medical Center (locations Sittard and Heerlen) in the period January 2016 to October 2016. The medical ethics committee METC Z (Medisch Ethische Toetsings Commissie van Zuyderland en Zuyd Hogeschool, Zuyderland Medical Center, Heerlen) approved this study.

Patients over 60 years admitted to Zuyderland were elegible for enrollment. Patients who presented with a delirium upon admission were excluded.

In the study wherein the DEMO was developed, an incidence rate of 17.4% was used [4]. On the assumption of the same sensitivity of 0.75 (75%), we calculated that 33 delirium patients were needed based upon the requirement that the lower limit of 95% CI would be 60%. With regard to the specificity, the number of non-delirium patients would be much larger than the number of delirium patients, and hence the width of the 95% confidence interval (CI) for specificity would be smaller than 0.30.

It was calculated that at least 332 patients would be needed to be able to identify 33 delirium patients. Taking into account the exclusion criteria and the possibility of a smaller percentage of patients who would develop a delirium, enough patients were screened to achieve the number of 33 delirium patients (i.e. 450 patients).

The DEMO carries out a daily analysis of all hospitalised patients ≥ 60 years of age in the different wards and predicts whether a patient is at risk of developing a delirium in the 24hours post analysis. The EPR (Electronic Patient Record) was accessed at a later date to confirm the delirium diagnosis by a physician. In this study, DEMO was calculated prospectively, but the outcome was ascertained by chart review retrospectively.

For validation purposes, the 450 DEMO patients were randomly selected (using https://www.randomlists.com/team-generator). An extraction from the EPR of these patients was made between 31-12-2015 and 31-10-2016.

A search in the EPR was performed per patient and date by using the following search terms: "delirium", "delirious", “agitation”, “agitated”, “confused”, “confusion”, “restlessness”, “disturbed”, “disorientation”, “disoriented”, “apathy”, “hallucination”, “mistrust”, “haloperidol”, , and “delirium prevention measures”. These search terms had been discussed with an internist geriatrician, a professor of old age medicine and a professor of geriatric psychiatry. Afterwards, this search was compared with the risk score from DEMO to evaluate whether the prediction was good (risk ≥ 14.1% [4]), which means that the diagnosis (search terms) was used as a reference to test DEMO’s screening characteristics. In this way, they were classified as True Positive (TP), True Negative (TN), False Positive (FP), False Negative (FN).
This evaluation was performed on different sets in order to evaluate the predictive value of the DEMO model as it had been developed (delirium within 24 hours), and to investigate whether other sets would give better results:

SET 1: “delirium" or "delirious" as diagnosis within 1 day after the DEMO analysis.
SET 2: “delirium" or "delirious" as diagnosis within 3 days after the DEMO analysis.
SET 3: “delirium" or "delirious" as diagnosis within 5 days after the DEMO analysis.
SET 4: "delirium", "delirious", “agitation”, “agitated”, “confused”, “confusion”, “restlessness”, “disturbed”, “disorientation”, “disoriented”, “apathy”, “hallucination”, “mistrust” or “haloperidol” as diagnosis within 5 days after the DEMO analysis.

The search was performed by first identifying where the different words appeared in the EPR and then the whole text was read and interpreted by two authors to ensure that it was truly a delirium diagnosis. If the results of the diagnostic test (TP / TN / FP / FN) could not be established for a patient as a result of unclear data, this patient was excluded from the analysis (e.g. differential diagnosis delirium, delirium? Patient seems confused, etc.). During the study, physicians were blinded to DEMO scores in order to avoid bias. The sensitivity, specificity and likelihood ratios with corresponding 95% confidence intervals were calculated with the use of an online calculator (http://vassarstats.net/clin1.html).

The differences in age and gender between delirium and non-delirium groups were tested by using the independent samples t-test and chi-square test, respectively. IBM SPSS statistics for Windows (version 23.0) was used to perform these tests. A two-sided p-value smaller than or equal to 0.05 was considered statistically significant.

RESULTS

The study lasted eight months and a total of 383 patients were included (figure 1 - supplementary figure). Each set was independently analysed. The results of the diagnostic test (TP/FP/FN/TN) for sets 1-4 are shown in Table 3 (supplementary tables). The analysis for all 4 sets, including prevalence estimates, sensitivity, specificity, and likelihood ratios, is presented in Table 4 (supplementary tables).

Set 1, set 2 and set 3 showed an increasing sensitivity and specificity, while set 4 showed a higher specificity and lower sensitivity.

Taking into account what we considered to be clinically relevant, set 3 was the most advantageous as the number of FN remained relatively small and the number of FP decreased in comparison to set 1 and set 2; in addition, the amount of FN is higher on set 4. In other words, we choose a higher sensitivity over a higher specificity given the consequences of missing a potential delirium compared to the consequences of falsely predicting a delirium. In the case of falsely predicting a delirium, non-pharmacological measures would be applied, which means that “unnecessary” attention is given to these patients.

The baseline characteristics for set 3 (age and gender) are shown in Table 1 (supplementary tables).

Table 1. Baseline characteristics SET 3

	Delirium (n = 50)	Non-delirium (n = 333)	Total (n = 383)
Mean age (SD)	84.7 (8.1) *	74.1 (9.1) *	75.5 (9.6)
Man	26 (52.0%)	168 (50.5%)	194 (50.7%)

* Statistically significant

A statistically significant difference between delirium and non-delirium patients was found in mean age (equal variances assumed, p <0.001, mean difference = 10.6, 95%CI 7.9 to 13.3). There was no significant difference in percentage of delirium between men and women (p = 0.176).

DISCUSSION AND CONCLUSION

In the current study, a previously developed model for predicting delirium has been validated; DEMO was calculated prospectively, and the outcome was ascertained by chart review retrospectively. Based on the current data and the high sensitivity and specificity, it can be concluded that the DEMO is a satisfactory prediction model.

Another strength of the DEMO model is that it predicts delirium on a daily basis. This is a novel concept as most delirium prediction rules work at admission but not daily. Even though it is not clear whether there is a definite advantage to predicting delirium on a daily basis, as this could lead to information overload, it could eventually be something that is tracked along with the vital signs and intake/output.

We found sensitivity and specificity rates that were higher than reported in the study of de Wit et al., which may be due to the fact that that study had only checked the patients' medical history for delirium and not the entire EPR. Moreover, de Wit et al. had performed the search merely on the word "delirium" and in the current study a wider set of search terms was used. Furthermore, in the current study, in those cases where a delirium was not clear, these patients were excluded, whereas such patients had been included in the development of the delirium model [4].

The present study does present some limitations. First of all, the validation of the DElirium MOdel depends on how and when a physician reports that a patient has developed a delirium. It is well known that documentation of delirium is poor since the majority of delirium remains unrecognised by the clinical teams [43]. We therefore performed a wider search using other words that might suggest delirium; however, this method resulted in more FN. Nevertheless, the DEMO is a merely an aid to detect delirium, not a diagnostic tool in itself. Furthermore, the number of delirium patients may still be rather low; although for sets 2-3 it is higher than originally planned.
Another limitation of the present study is that this is a single centre study located in the Netherlands and may not be generalizable in other settings.

The DEMO only uses electronically available data. Other important factors that could predict a delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because they were not electronically available. If this data would also be made electronically available, the predictive quality of DEMO could be improved [22, 23, 28, 38]. Taking into account that the registration of such factors is becoming increasingly important and mandatory, it is only a matter of time until these important factors can be used in the DEMO [2,3]. In addition, DEMO already uses a clever way of identifying cognitive impairment by including medications used for dementia.

DElirum MOdel is a fully automated satisfactory prediction model. The next step is to validate the DEMO in a cohort where the outcome of delirium would be prospectively assessed in person, and the DEMO model used for retrospective measurements. In the future DEMO will be applied in clinical practice so that physicians are alerted when a patient is at increased risk of developing delirium. This will facilitate earlier recognition and diagnosis and thus prevention measures can be implemented.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from ABC Company for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

FUNDING

This work was supported by ZonMw (the Netherlands Organisation for Health Research and Development) grant number [113101001]

AUTHORS' CONTRIBUTIONS

All authors have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; They all have been involved in drafting the manuscript and revising it critically for important intellectual content; They all have given final approval of the version to be published; and they all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conception or design of the work

C Mestres Gonzalvo
HAJM de Wit
BPC van Oijen
DS Deben
KPGM Hurkens
WJ Mulder
R Janknegt
JMGA Schols
FR Verhey
B Winkens
PHM van der Kuy

Data collection

C Mestres Gonzalvo
DS Deben

Data analysis and interpretation

C Mestres Gonzalvo
FR Verhey
B Winkens
PHM van der Kuy

Drafting the article

C Mestres Gonzalvo

Critical revision of the article

HAJM de Wit

BPC van Oijen

JMGA Schols

FR Verhey

B Winkens

PHM van der Kuy

Final approval of the version to be published

C Mestres Gonzalvo

HAJM de Wit

BPC van Oijen

DS Deben

KPGM Hurkens

WJ Mulder

R Janknegt

JMGA Schols

FR Verhey

B Winkens

PHM van der Kuy

TRANSPARENCY DECLARATION

C. Mestres Gonzalvo affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING

All data is anonymized and will be confidentially handled. Only the investigators have access to the data.

All patient data will be kept for as long as the project is being conducted.

EXCLUSIVE LICENCE

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the publishers.

(http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.doc)

REFERENCES

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-22.
2. Delirium: Diagnosis, prevention and management. NICE guidelines [CG103] Published date: July 2010
3. Delirium for adults Dutch guideline. Richtlijn Delier Volwassenen. Nederlandse Vereniging voor Klinische Geriatrie (NVKG) 2013
4. Hugo AJM de Wit, Bjorn Winkens, Carlota Mestres Gonzalvo, Kim PGM Hurkens, Wubbo J Mulder, Rob Janknegt, Frans R Verhey, Paul-Hugo M van der Kuy, and Jos MGA Schols. The development of an automated ward independent delirium risk prediction model. Int J Clin Pharm (2016) 38:915–923
5. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35(4):350-64.
6. Ryan DJ, O'Regan NA, Caoimh RÓ, et al: Delirium in an adult acute hospital population: predictors, prevalence and detection. BMJ Open 2013; 3(1). http://dx.doi.org/10.1136/bmjopen-2012-001772
7. Inouye SK. Delirium in hospitalized older patients. Clin. Geriatr. Med. 1998;14:745–764.
8. Bruce, A. J., Ritchie, C. W., Blizard, R., Lai, R. & Raven, P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. Int. Psychogeriatr. 19, 197-214 (2007).
9. Girard, T. D. & Ely, E. W. Delirium in the critically ill patient. Handb. Clin. Neurol. 90, 39-56 (2008)
10. Inouye SK. Delirium in older persons. N. Engl. J. Med. 2006;354:1157–1165
11. Pisani, M. A., McNicoll, L. & Inouye, S. K. Cognitive impairment in the intensive care unit. N. Engl. J. Med. 24, 727-737 (2003)
12. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008 Jan 14;168(1):27-32. PubMed PMID: 18195192.
13. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
14. WHO Regional Offi ce for Europe. European hospital morbidity database. Copenhagen: World Health Organization, 2012.
15. Organisation for Economic Co-operation and Development. OECD health data 2012. Paris: Organisation for Economic Co-operation and Development, 2012.
16. Adamis D, Sharma N, Whelan PJ, Macdonald AJ. Delirium scales: a review of current evidence. Aging Ment Health 2010; 14: 543–55.
17. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA 2010; 304: 779–86.
18. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec 15;113(12):941-8. PubMed PMID: 2240918. Epub 1990/12/15.
19. Jin H. Han MD, MSc1,and Eduard E. Vasilevskis. Ultrabrief delirium assessments—are they ready for primetime? DOI: 10.1002/jhm.2478

20. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pract. 2003 Spring;17(1):31-50. PubMed PMID: 12751884. Epub 2003/05/20.
21. van Velthuijsen EL, et al. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. Int J Geriatr Psychiatry. 2016 Sep;31(9):974-89. doi: 10.1002/gps.4441. Epub 2016 Feb 21.
22. 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):249-54. PubMed PMID: 18707947. Epub 2008/08/19.
23. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord. 1999 Sep-Oct;10(5):393-400. PubMed PMID: 10473946. Epub 1999/09/04.
24. AGS/NIA Delirium Conference Writing Group PC, Faculty: The American Geriatrics Society/National Institute on Aging Bedside-to-Bench Conference: Research Agenda on Delirium in Older Adults. Journal of the American Geriatrics Society 2015, 63(5):843-852.
25. Flaherty JH, Gonzales JP, Dong B: Antipsychotics in the treatment of delirium in older hospitalized adults: a systematic review. Journal of the American Geriatrics Society 2011, 59 Suppl 2:S269-276.
26. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM: Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society 2016, 64(4):705-714.
27. Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. Neurotherapeutics. 2012 Jan;9(1):158-75. doi: 10.1007/s13311-011-0102-9.
28. Young J, Leentjens AF, George J, Olofsson B, Gustafson Y. Systematic approaches to the prevention and management of patients with delirium. J Psychosom Res. 2008 Sep;65(3):267-72. PubMed PMID: 18707950.
29. Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. Psychosomatics. 2013 Mar-Apr;54(2):124-31. PubMed PMID: 23380670.
30. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005 Oct;53(10):1658-66. PubMed PMID: 16181163.
31. Wang W1, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, Chen KS, Gu XE, Zhu SN. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. Crit Care Med. 2012 Mar;40(3):731-9. doi: 10.1097/CCM.0b013e3182376e4f.
32. Anne JH Vochteloo, Sophie Moerman, Boudewijn LS Borger van der Burg, Maarten de Boo, Mark R de Vries, Dieu-Donné Niesten, Wim E Tuinebreijer, Rob GHH Nelissen and Peter Pilot. Delirium risk screening and haloperidol prophylaxis program in hip fracture patients is a helpful tool in

identifying high-risk patients, but does not reduce the incidence of delirium. BMC Geriatrics 2011, 11:39 doi:10.1186/1471-2318-11-39

33. Schrader SL, Wellik KE, Demaerschalk BM, Caselli RJ, Woodruff BK, Wingerchuk DM. Adjunctive haloperidol prophylaxis reduces postoperative delirium severity and duration in at-risk elderly patients. Neurologist 2008;14:134-7.

34. van den Boogaard M, Schoonhoven L, van Achterberg T, et al: Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Crit Care 2013; 17:R9

35. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2016 Apr;64(4):705-14. doi: 10.1111/jgs.14076.

36. E.J.M. Schrijver et al. Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: A systematic review of current evidence. European Journal of Internal Medicine 27 (2016) 14–23

37. Hshieh et al. JAMA Intern Med. 2015;175(4):512-520. doi:10.1001/jamainternmed.2014.7779

38. Kishi T, et al. J Neurol Neurosurg Psychiatry 2016;87:767–774. doi:10.1136/jnnp-2015-311049

39. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012;344:e420. PubMed PMID: 22323509. Pubmed Central PMCID: 3276486.

40. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med. 1993 Sep 15;119(6):474-81. PubMed PMID: 8357112.

41. Carrasco MP, Villarroel L, Andrade M, et al. Development and validation of a delirium predictive score in older people. Age Ageing. 2014;43(3):346-51.

42. Douglas VC, Hessler CS, Dhaliwal G, et al. The AWOL tool: derivation and validation of a delirium prediction rule. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2013;8(9):493-9.)

43. Collins N, Blanchard MR, Tookman A, Sampson EL: Detection of delirium in the acute hospital. Age Ageing 2010, 39(1):131-135.

Figure 1. Flow diagram inclusion

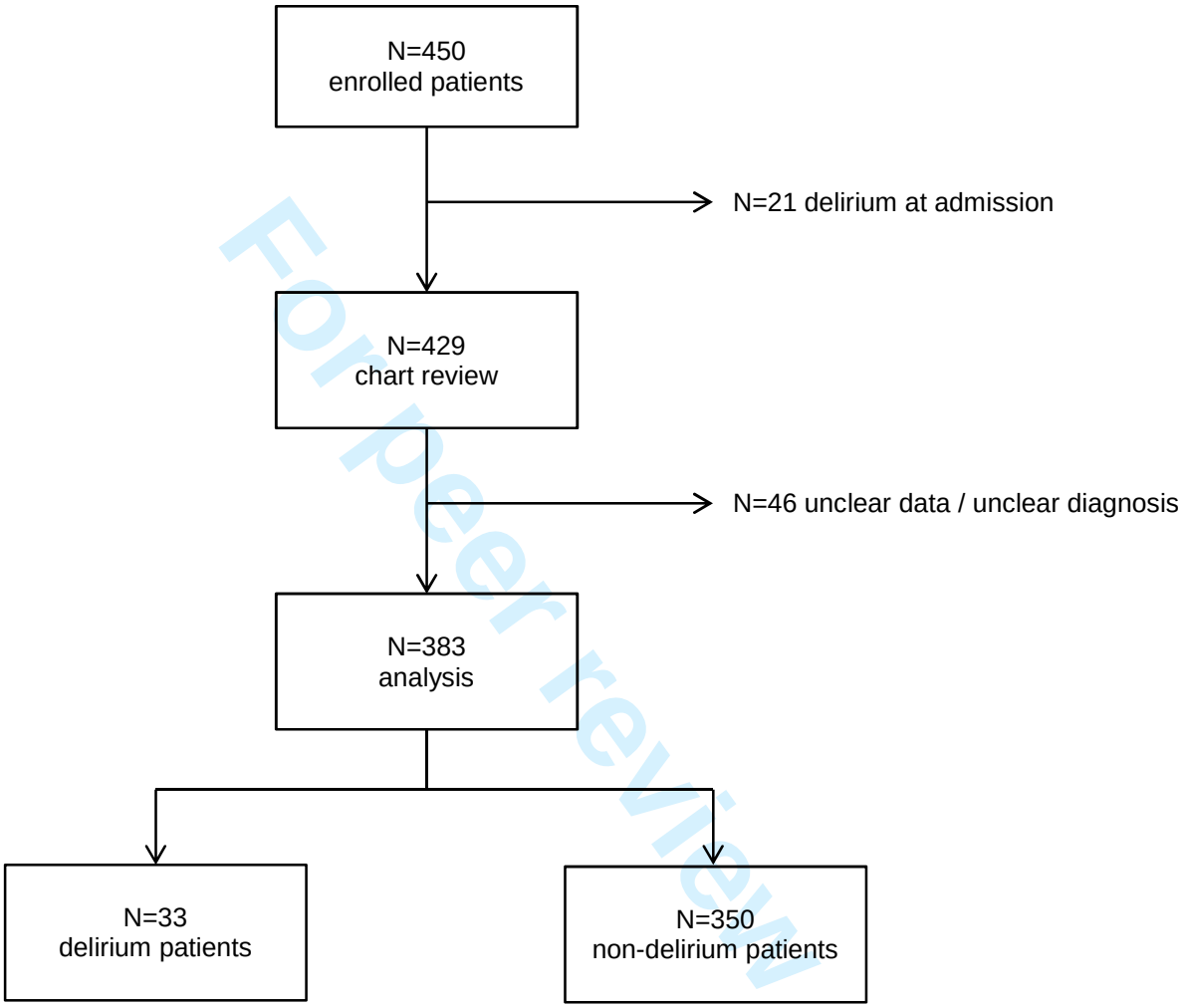


Table 2. DElirium MOdel and cut-off point

DEMO-score = 1/(1+e-(Linear predictor)) DEMO score > 14,1% → Risk at delirium DEMO score ≤ 14,1% → No risk at delirium
Linear predictor = -8,823 + (0,081*V1) + (0,031*V2) + (0,248*V3) + (1,123*V4) + (0,286*V5) + (1,963*V6) + (0,359*V7) + (1,199*V8) + (0,413*V9) + (0,103*V10) V1 = Age (years) V2 = Polypharmacy ATC-5th V3 = Anxiolytics (N05B) V4 = Anti-dementia (N06D) V5 = Antidepressives (N06A) V6 = Antiparkinson's (N04) V7 = Antidiabetic's (A10) V8 = Psychopharmaca (N05A) V9 = Analgetics (N02A) V10 = Sleepmedication (N05C)

Table 3. Cross-table of the predicted test result of the prediction model (DEMO positive or negative) and diagnosis (delirium positive or negative) per set.

	SET 1		SET 2		SET 3		SET 4	
	Delirium positive	Delirium negative	Delirium positive	Delirium negative	Delirium positive	Delirium negative	Delirium positive	Delirium negative
DEMO Positive	29	96	40	85	46	79	82	45
DEMO Negative	4	254	4	254	4	254	16	240

Table 4. Estimates of the prevalence, sensitivity, specificity, and likelihood ratios with corresponding 95% confidence intervals per set.

	SET 1			SET 2			SET 3			SET 4		
	Estimated value	95% confidence interval		Estimated value	95% confidence interval		Estimated value	95% confidence interval		Estimated value	95% confidence interval	
		Lower limit	Upper limit		Lower limit	Upper limit		Lower limit	Upper limit		Lower limit	Upper limit
Prevalence	0.086 (8.6%)	0.061	0.120	0.115 (11.5%)	0.086	0.152	0.131 (13.1%)	0.099	0.169	0.256 (25.6%)	0.213	0.303
ensitivity	0.879 (87.9%)	0.709	0.960	0.909 (90.9%)	0.774	0.971	0.920 (92.0%)	0.799	0.974	0.837 (83.7%)	0.745	0.901
pecificity	0.726 (72.6%)	0.675	0.771	0.749 (74.9%)	0.699	0.794	0.763 (76.3%)	0.713	0.807	0.842 (84.2%)	0.793	0.881
+LR	3.204	2.59	3.962	3.626	2.950	4.457	3.878	3.146	4.780	1.822	1.394	2.382
-LR	0.167	0.067	0.419	0.121	0.048	0.310	0.105	0.041	0.269	0.067	0.041	0.107

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5	
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	4-5	
Bias	9	Describe any efforts to address potential sources of bias	-	
Study size	10	Explain how the study size was arrived at	4	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	Table 2
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	5-6
		(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	Table 3
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2
		(*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	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
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	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-7
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
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	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Validation of an automated delirium prediction model (DEMO Delirium Model): an observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016654.R2
Article Type:	Research
Date Submitted by the Author:	05-Jul-2017
Complete List of Authors:	Mestres Gonzalvo, Carlota; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology de Wit, Hugo; Zuyderland Medisch Centrum Heerlen, Clinical Pharmacy, Pharmacology and Toxicology van Oijen, Brigit; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Debben, Debbie; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Hurkens, Kim; Zuyderland Medisch Centrum Heerlen, Geriatric Medicine, Department of Internal Medicine Mulder, Wubbo; Maastricht Universitair Medisch Centrum+, Internal Medicine Janknegt, Rob; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Schols, Jos; Maastricht University, Department of General Practice, School for Public Health and Primary Care (CAPHRI) Verhey, Frans; Maastricht University Faculty of Health Medicine and Life Sciences, Psychiatry and Neuropsychology, Alzheimer Centrum Limburg / School for Mental Health and Neurosciences Winkens, Bjorn; Maastricht University, van der Kuy, Hugo; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Mental health
Keywords:	GERIATRIC MEDICINE, Delirium & cognitive disorders < PSYCHIATRY, PSYCHIATRY

Validation of an automated delirium prediction model (DEMO Delirium Model):
an observational study

C Mestres Gonzalvo (hospital pharmacist)[1,2], HAJM de Wit (hospital pharmacist)[1], BPC van Oijen (hospital pharmacist)[1], D Deben (hospital pharmacist in training)[1], KPGM Hurkens (internist geriatrician)[3], WJ Mulder (internist geriatrician)[4], R Janknegt (hospital pharmacist)[1], JMGA Schols (Professor of Old Age Medicine)[5], FR Verhey (Professor of Geriatric Psychiatry)[6], B Winkens (statistician)[7], PHM van der Kuy (clinical pharmacologist)[1]

[1]Department of Clinical Pharmacy, Pharmacology and Toxicology, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen, The Netherlands.
[2]Department of Clinical Pharmacy, Elkerliek Hospital, Wesselmanlaan 25, 5707 HA Helmond, The Netherlands.
[3]Section of Geriatric Medicine, Department of Internal Medicine, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen The Netherlands.
[4]Department of Internal Medicine, Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands.
[5]Department of Family Medicine and Department of Health Services Research, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[6]Department of Psychiatry and Neuropsychology, Alzheimer Centrum Limburg/School for Mental Health and Neurosciences, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[6]Department of Methodology and Statistics, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyeplein 1, 6229 HA Maastricht, The Netherlands.

Submitting and corresponding author:
Carlota Mestres Gonzalvo
Department of Clinical Pharmacy, Pharmacology and Toxicology
Zuyderland Medical Centre
Dr H van der Hoffplein 1
6162 BG Sittard-Geleen
Phone: +31-88-4597708
E-mail: c.mestresgonzalvo@zuyderland.nl

ABSTRACT

Objectives: Delirium is an under-diagnosed, severe, and costly disorder, and 30-40% of cases can be prevented. A fully automated model to predict delirium (DEMO) in older people has been developed, and the objective of this study is to validate the model in a hospital setting.

Setting: Secondary care, one hospital with two locations

Design: Observational study

Participants: The study included 450 randomly selected patients over 60 years of age admitted to Zuyderland Medical Centre. Patients who presented with delirium upon admission were excluded.

Primary outcome measures: Development of delirium through chart review.

Results: A total of 383 patients were included in this study. The analysis was performed 1, 3 and 5 days after a DEMO score was obtained. Sensitivity was 87.1% (CI: 0.756 to 0.939), 86.3% (CI: 0.763 to 0.926), and 83.7% (0.7945to 0.901) for 1, 3, and 5 days, respectively, after obtaining the DEMO score. Specificity was 77.9% (0.729 to 0.882), 81.5% (0.766 to 0.856) and 84.2% (0.793 to 0.881) for 1, 3, and 5 days, respectively, after obtaining the DEMO score.

Conclusion: DEMO is a satisfactory prediction model but needs further prospective validation with in-person delirium confirmation. In the future, DEMO will be applied in clinical practice so that physicians will be aware of when a patient is at an increased risk of developing delirium, which will facilitate earlier recognition and diagnosis, and thus will allow the implementation of prevention measures.

Strengths and limitations of this study

- A high risk of delirium can be predicted electronically by using DEMO (DElirium MOdel) with reasonably good sensitivity and specificity.
- DEMO can be applied in clinical practice to facilitate earlier recognition and diagnosis of delirium.
- Important factors that could predict delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because these data are not yet electronically available.

INTRODUCTION

A delirium or acute confused state is a transient attention and cognition disorder that develops over a short period of time and occurs mainly in hospitalised patients and people aged 60 years and over. Delirium is an under-diagnosed, severe (increased mortality), costly and often preventable disorder [1-3]. Its severity and symptoms can vary considerably, but the main features are impaired cognitive and sensory functions, reduced consciousness, and diminished attention. In addition, it is often accompanied by problems with psychomotor activity, the circadian rhythm, and emotions.

The prevalence and incidence of delirium in the general population differ widely depending on the setting. The overall prevalence in the community is estimated to be 1-2%. In a hospital setting, this prevalence increases to 10-31% at the time of hospital admission and 3-29% during hospitalisation. The incidence increases up to 87% when more specialised populations, such as the elderly and people in postoperative, intensive care and/or palliative care, are considered [4-11]. In 30-40% of cases, delirium is preventable, which, along with its associated high costs (ranging from US$164 billion to US$182 billion per year), makes it a perfect target for interventions by healthcare professionals [1, 4, 12-15]. As a result, a great number of screening tools have been developed and are widely used to detect the early onset of delirium, which can in turn allow treatment measures to be introduced in a timely manner [16-21]. These tools help healthcare professionals to establish and quantify symptoms associated with delirium [19-23]. Once the diagnosis has been established, the underlying medical condition can be targeted, and delirium can be managed appropriately.

There is no effective treatment for delirium [24, 25]. Preventing delirium is by far a more effective strategy to improve patient outcomes [1, 4, 26-29]. Risk models have been used to identify patients at higher risk for delirium development because these patients would most likely benefit from delirium prevention. These models are based on manual evaluation of individual risk factors and may be difficult to implement, so automated models are preferable and more feasible [30-34].

Screening instrument

A fully automated model to predict delirium in older people (over 60 years) was developed at Zuyderland Medical Centre. This DElirium MOdel (DEMO) uses only electronically available data to predict the occurrence of delirium. The predictive variables include age; polypharmacy; and the use of anti-dementia drugs, antidepressants, anti-Parkinson's agents, anti-diabetic drugs, analgesia and/or sleeping tablets (see Table 1 (supplementary tables)). This model can be applied hospital-wide and has an area under receiver operating characteristic (AUROC: measure for model prediction quality) value of 0.770 (95% CI 0736-0804) with a sensitivity of 78.2% and a specificity of 63.7%, when 14.1% is used as a cut-off value for the predicted probability of developing delirium. DEMO was developed retrospectively but has not yet been validated [4].

Therefore, the objective of this study is to validate DEMO in a hospital setting. To do so, the system's accuracy (main study parameter), i.e., sensitivity (proportion of delirium patients who test positive)

and specificity (proportion of non-delirium patients who test negative), will be calculated. In addition to these parameters, the positive and negative likelihood ratios with their 95% CI will be computed.

METHOD

This is an observational study of the ability of DEMO to predict delirium in an elderly hospital population. It was conducted in Zuyderland Medical Centre (locations Sittard and Heerlen) in the period from January 2016 to October 2016. The medical ethics committee METC Z (Medisch Ethische Toetsings Commissie van Zuyderland en Zuyd Hogeschool, Zuyderland Medical Centre, Heerlen) approved this study.

Patients over 60 years who were admitted to Zuyderland were eligible for enrolment. Patients who, based on chart review, presented with delirium upon admission were excluded.

At admission, patients are routinely screened for delirium, both in the emergency department and in the ward. The first screening is performed by a validated checklist (IGZ Inspectie voor de Gezondheidszorg = Dutch Healthcare Inspectorate, and VMS Veiligheidsmanagementsysteem = Safety Management System) [35]. The results from this checklist give an indication for the risk of developing delirium. When the risk is high, the DOSS method [20] is used to evaluate whether a patient has delirium.

In the study wherein the DEMO was developed, an incidence rate of 17.4% was used [4]. Given the assumption of the same sensitivity of 0.75 (75%), we calculated that 33 delirium patients were needed based upon the requirement that the lower limit of 95% CI would be 60%. With regard to the specificity, the number of non-delirium patients would be much larger than the number of delirium patients, and hence, the width of the 95% confidence interval (CI) for specificity would be smaller than 0.30.
It was calculated that at least 332 patients would be needed to identify 33 delirium patients. Taking into account the exclusion criteria and the possibility of a smaller percentage of patients who would develop delirium, a sufficient number of patients were screened to obtain 33 delirium patients (i.e., 450 patients).

DEMO involves a daily analysis of all hospitalised patients ≥ 60 years of age at the different wards and predicts whether a patient is at risk of developing delirium in a 24-hour post-analysis period. The EPR (Electronic Patient Record) was accessed at a later date to check for delirium diagnosis. In this study, DEMO was calculated prospectively, but the outcome was ascertained by chart review retrospectively.

For validation purposes, the 450 DEMO patients were randomly selected (using https://www.randomlists.com/team-generator). An extraction from the EPR of these patients was made between 31-12-2015 and 31-10-2016.

A search in the EPR was performed according to patient and date by using the following search terms: "delirium", "delirious", “agitation”, “agitated”, “confused”, “confusion”, “restlessness”, “disturbed”, “disorientation”, “disoriented”, “apathy”, “hallucination”, “mistrust”, “haloperidol”, and “delirium prevention measures”. These search terms were discussed with an internist geriatrician, a professor of geriatric medicine and a professor of geriatric psychiatry.
The search was performed by first identifying where the different words appeared in the EPR, and then, the whole EPR during the admission period was read and interpreted by two authors (KH (internist geriatrician) and CMG (hospital pharmacist)) to ensure that it was truly a delirium diagnosis. If the results of the diagnostic test (TP / TN / FP / FN) could not be established for a patient as a result of unclear data, this patient was excluded from the analysis (e.g., differential diagnosis delirium, potential delirium, patient seems confused). The date of delirium onset was determined by chart review.

Afterwards, this search was compared with the risk score from DEMO to evaluate whether the prediction was good (risk ≥ 14.1% [4]), which means that the diagnosis (search terms) was used as a reference to test DEMO’s screening characteristics. In this way, the predictions were classified as True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN).
The search was performed in the patients' charts in which different healthcare professionals such as physicians, nurses, physiotherapists, and speech therapists note their findings about a patient.

This evaluation was performed 1, 3 and 5 days after the DEMO analysis to evaluate the predictive value of DEMO as it had been developed (delirium within 24 hours) and to investigate whether its predictive value could be extended.

During the study, physicians were blinded to DEMO scores in order to avoid bias. The sensitivity, specificity and likelihood ratios with corresponding 95% confidence intervals were calculated with the use of an online calculator (http://vassarstats.net/clin1.html).

The differences in age and gender between delirium and non-delirium groups were tested by using the independent-samples t-test and chi-square test, respectively. IBM SPSS statistics for Windows (version 23.0) was used to perform these tests. A two-sided p-value smaller than or equal to 0.05 was considered statistically significant.

RESULTS

The study lasted eight months, and a total of 383 patients were included (Figure 1 - supplementary figure). The results of the diagnostic test (TP/FP/FN/TN) for 1, 3 and 5 days after DEMO analysis are shown in Table 2 (supplementary tables). The analysis, including prevalence estimates, sensitivity, specificity, and likelihood ratios, is presented in Table 3 (supplementary tables).

Sensitivity decreases over time and is the lowest (83.7%) on day 5 after DEMO analyses, and specificity increases over time and is the highest (84.2%) on day 5 after DEMO analysis.

The baseline characteristics (age and gender) are shown in Table 4 (supplementary tables).

Table 4. Baseline characteristics

	Delirium during admission			No-delirium during admission			Total
	Day 1 N=62	Day 3 N=80	Day 5 N=98	Day 1 N=321	Day 3 N=303	Day 5 N=385	N=383
Mean age (SD)	83.9 (7.8)*	83.7 (7.9)*	83.0 (8.5)*	73.9 (9.1)*	73.3 (8.8)*	72.9 (8.5)*	75.5 (9.6)*
Man	31 (50,0%)	38 (47,5%)	48 (49.0%)	163 (50.1%)	162 (53.5%)	165 (57.9%)	194 (50.7%)

* Statistically significant

A statistically significant difference in mean age was found between delirium and non-delirium patients for day 1, day 3 and day 5 after DEMO analysis (Day 1: equal variances assumed, $p<0.001$, mean difference=10.0, 95%CI 7.6 to 12.5, Day 3: equal variances assumed, $p<0.001$, mean difference=10.4, 95%CI 8.3 to 12.6, Day 5: equal variances assumed, $p<0.001$, mean difference=10.1, 95%CI 12.1 to 8.2). There was no significant difference in the percentage of delirium between men and women for day 1, day 3 nor day 5 after DEMO analysis ($p=0.911$, $p=0.597$, $p=0.701$ resp.).

DISCUSSION AND CONCLUSION

In the current study, a previously developed model for predicting delirium has been validated. DEMO was calculated prospectively, and the outcome was ascertained by chart review retrospectively. Based on the current data and the high sensitivity and specificity, it can be concluded that DEMO is a satisfactory prediction model.

Another strength of DEMO is that it predicts delirium on a daily basis. This is a novel concept, as most delirium prediction rules apply at admission but not daily. Even though it is not clear whether there is a definite advantage to predicting delirium on a daily basis, as this could lead to information overload, it could eventually be something that is tracked along with vital signs and intake/output.

We found sensitivity and specificity rates that were higher than reported in the study of de Wit et al., which may be because his study only checked the patients' medical history for delirium and not the

entire EPR. Moreover, de Wit et al. had performed the search merely on the diagnosis of delirium. In the current study, the full EPR during the admission period was taken into account, and a wider set of terms was considered for delirium diagnosis. Furthermore, in the current study, in those cases in which delirium was not clear, these patients were excluded, whereas such patients had been included in the development of the delirium model [4].

The present study does present some limitations. First, the validation of the DElirium MOdel depends on how and when a healthcare professional reports that a patient has developed delirium. It is well known that documentation of delirium is poor since the majority of delirium remains unrecognised by clinical teams [36]. We therefore performed a wider search considering other words that might suggest delirium as delirium diagnosis and read through the whole EPR during the admission period. The number of delirium patients is noticeably higher than originally found, which can be explained by the search we performed. The DEMO is merely an aid to detect delirium, not a diagnostic tool by itself.

In addition, as mentioned in the study by Inouye et al. [37], using a chart review method has some limitations. As mentioned in their study, the fact that validated checklists are used to screen for delirium and that the chart is a complete document in which different healthcare professionals note their findings makes the outcome more reliable and strengthens the validity of the present study. Nevertheless, it is possible that patients with delirium at admission may have been included in the non-delirious cohort due to poor documentation in the chart.

Another limitation of the present study is that this is a single-centre study (two hospital locations) located in the Netherlands and may not be generalisable in other settings.

The DEMO uses only electronically available data. Other important factors that could predict a delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because they were not electronically available. If these data were also made electronically available, the predictive quality of DEMO could be improved [22, 23, 27, 30]. Taking into account that the registration of such factors is becoming increasingly important and mandatory, it is only a matter of time until these important factors can be used in the DEMO [2, 3]. In addition, DEMO already uses an alternative way of identifying cognitive impairment by including medications used for dementia.

The DElirium MOdel is a fully automated satisfactory prediction model that predicts delirium up to 5 days after analysis. The next step is to validate the DEMO in a cohort in which the outcome of delirium would be prospectively assessed in person and to use DEMO for retrospective measurements. In the future, DEMO will be applied to clinical practice so that physicians are alerted when a patient is at increased risk of developing delirium. This will facilitate earlier recognition and diagnosis and, thus, the implementation of prevention measures.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from ABC Company for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

FUNDING

This work was supported by ZonMw (the Netherlands Organisation for Health Research and Development) grant number [113101001]

AUTHORS' CONTRIBUTIONS

All authors have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; They all have been involved in drafting the manuscript and revising it critically for important intellectual content; They all have given final approval of the version to be published; and they all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conception or design of the work

C Mestres Gonzalvo
HAJM de Wit
BPC van Oijen
DS Deben
KPGM Hurkens
WJ Mulder
R Janknegt
JMGA Schols
FR Verhey
B Winkens
PHM van der Kuy

Data collection

C Mestres Gonzalvo
DS Deben
KPGM Hurkens

Data analysis and interpretation

C Mestres Gonzalvo

KPGM Hurkens

FR Verhey

B Winkens

PHM van der Kuy

Drafting the article

C Mestres Gonzalvo

Critical revision of the article

HAJM de Wit

BPC van Oijen

JMGA Schols

FR Verhey

B Winkens

PHM van der Kuy

Final approval of the version to be published

C Mestres Gonzalvo

HAJM de Wit

BPC van Oijen

DS Deben

KPGM Hurkens

WJ Mulder

R Janknegt

JMGA Schols

FR Verhey

B Winkens

PHM van der Kuy

TRANSPARENCY DECLARATION

C. Mestres Gonzalvo affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING

All data is anonymized and will be confidentially handled. Only the investigators have access to the data.

All patient data will be kept for as long as the project is being conducted.

EXCLUSIVE LICENCE

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the publishers.

(http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.doc)

REFERENCES

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-22.
2. Delirium: Diagnosis, prevention and management. NICE guidelines [CG103] Published date: July 2010
3. Delirium for adults Dutch guideline. Richtlijn Delier Volwassenen. Nederlandse Vereniging voor Klinische Geriatrie (NVKG) 2013
4. Hugo AJM de Wit, Bjorn Winkens, Carlota Mestres Gonzalvo, Kim PGM Hurkens, Wubbo J Mulder, Rob Janknegt, Frans R Verhey, Paul-Hugo M van der Kuy, and Jos MGA Schols. The development of an automated ward independent delirium risk prediction model. Int J Clin Pharm (2016) 38:915–923
5. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35(4):350-64.
6. Ryan DJ, O'Regan NA, Caoimh RÓ, et al: Delirium in an adult acute hospital population: predictors, prevalence and detection. BMJ Open 2013; 3(1). http://dx.doi.org/10.1136/bmjopen-2012-001772
7. Inouye SK. Delirium in hospitalized older patients. Clin. Geriatr. Med. 1998;14:745–764.
8. Bruce, A. J., Ritchie, C. W., Blizard, R., Lai, R. & Raven, P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. Int. Psychogeriatr. 19, 197-214 (2007).
9. Girard, T. D. & Ely, E. W. Delirium in the critically ill patient. Handb. Clin. Neurol. 90, 39-56 (2008)
10. Inouye SK. Delirium in older persons. N. Engl. J. Med. 2006;354:1157–1165
11. Pisani, M. A., McNicoll, L. & Inouye, S. K. Cognitive impairment in the intensive care unit. N. Engl. J. Med. 24, 727-737 (2003)
12. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008 Jan 14;168(1):27-32. PubMed PMID: 18195192.
13. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
14. WHO Regional Offi ce for Europe. European hospital morbidity database. Copenhagen: World Health Organization, 2012.

15. Organisation for Economic Co-operation and Development. OECD health data 2012. Paris: Organisation for Economic Co-operation and Development, 2012.
16. Adamis D, Sharma N, Whelan PJ, Macdonald AJ. Delirium scales: a review of current evidence. Aging Ment Health 2010; 14: 543–55.
17. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA 2010; 304: 779–86.
18. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec 15;113(12):941-8. PubMed PMID: 2240918. Epub 1990/12/15.
19. Jin H. Han MD, MSc1,and Eduard E. Vasilevskis. Ultrabrief delirium assessments—are they ready for primetime? DOI: 10.1002/jhm.2478
20. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pract. 2003 Spring;17(1):31-50. PubMed PMID: 12751884. Epub 2003/05/20.
21. van Velthuijsen EL, et al. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. Int J Geriatr Psychiatry. 2016 Sep;31(9):974-89. doi: 10.1002/gps.4441. Epub 2016 Feb 21.
22. 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):249-54. PubMed PMID: 18707947. Epub 2008/08/19.
23. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord. 1999 Sep-Oct;10(5):393-400. PubMed PMID: 10473946. Epub 1999/09/04.
24. AGS/NIA Delirium Conference Writing Group PC, Faculty: The American Geriatrics Society/National Institute on Aging Bedside-to-Bench Conference: Research Agenda on Delirium in Older Adults. Journal of the American Geriatrics Society 2015, 63(5):843-852.
25. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM: Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society 2016, 64(4):705-714.
26. Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. Neurotherapeutics. 2012 Jan;9(1):158-75. doi: 10.1007/s13311-011-0102-9.
27. Young J, Leentjens AF, George J, Olofsson B, Gustafson Y. Systematic approaches to the prevention and management of patients with delirium. J Psychosom Res. 2008 Sep;65(3):267-72. PubMed PMID: 18707950.
28. Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. Psychosomatics. 2013 Mar-Apr;54(2):124-31. PubMed PMID: 23380670.
29. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005 Oct;53(10):1658-66. PubMed PMID: 16181163.

30. Kishi T, et al. J Neurol Neurosurg Psychiatry 2016;87:767–774. doi:10.1136/jnnp-2015-311049
31. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012;344:e420. PubMed PMID: 22323509. Pubmed Central PMCID: 3276486.
32. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med. 1993 Sep 15;119(6):474-81. PubMed PMID: 8357112.
33. Carrasco MP, Villarroel L, Andrade M, et al. Development and validation of a delirium predictive score in older people. Age Ageing. 2014;43(3):346-51.
34. Douglas VC, Hessler CS, Dhaliwal G, et al. The AWOL tool: derivation and validation of a delirium prediction rule. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2013;8(9):493-9.)
35. http://www.vmszorg.nl/ (Visited on 20/6/2017)
36. Collins N, Blanchard MR, Tookman A, Sampson EL: Detection of delirium in the acute hospital. Age Ageing 2010, 39(1):131-135.
37. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST, Jr., Leslie DL, Agostini JV: A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. Journal of the American Geriatrics Society 2005, 53(2):312-318.

Figure 1. Flow diagram inclusion

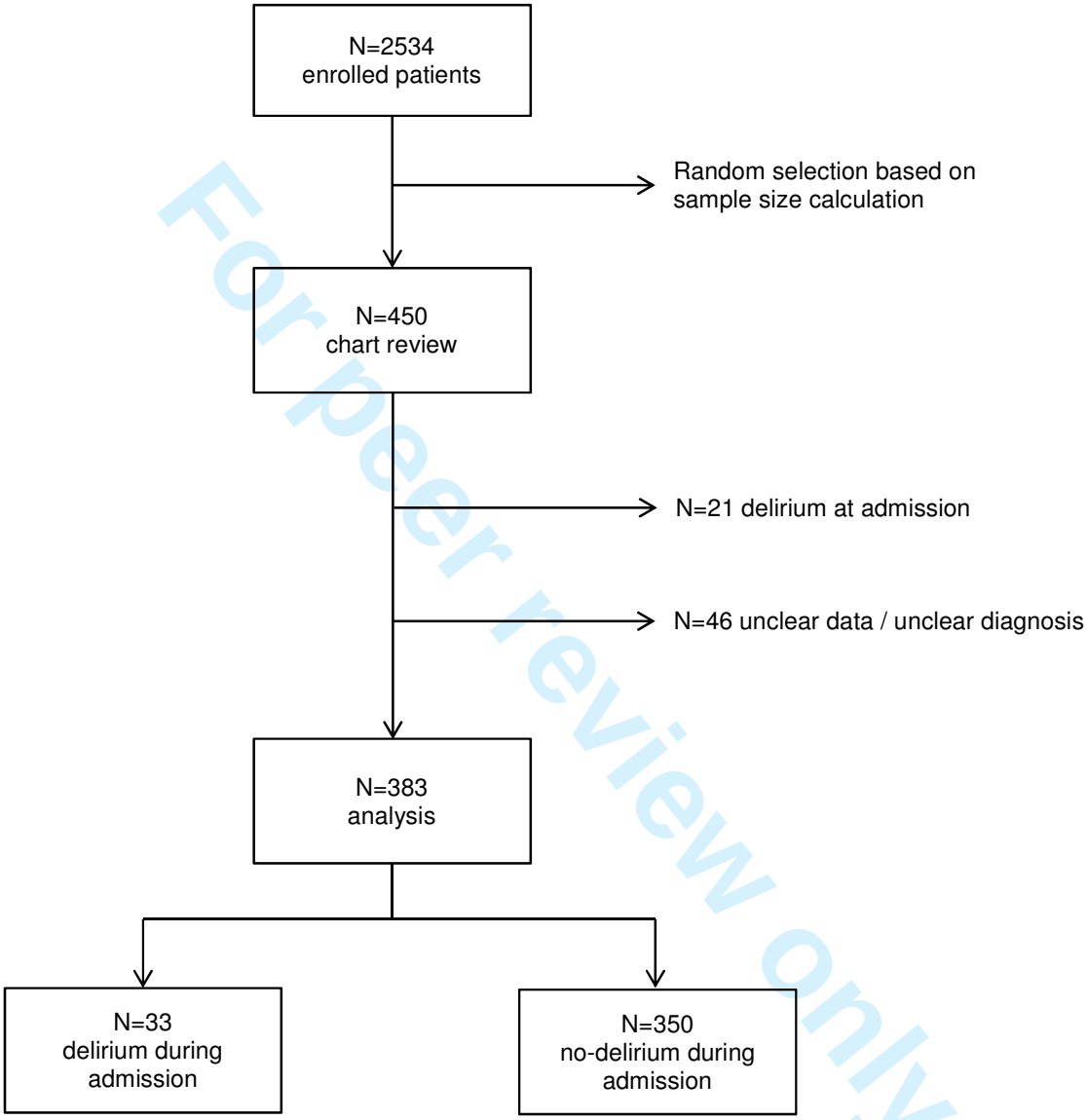


Table 1. DElirium MOdel and cut-off point

DEMO-score = 1/(1+e-(Linear predictor)) DEMO score > 14,1% → Risk at delirium DEMO score ≤ 14,1% → No risk at delirium
Linear predictor = -8,823 + (0,081*V1) + (0,031*V2) + (0,248*V3) + (1,123*V4) + (0,286*V5) + (1,963*V6) + (0,359*V7) + (1,199*V8) + (0,413*V9) + (0,103*V10) V1 = Age (years) V2 = Polypharmacy (number of drugs) V3 = Anxiolytics (ATC N05B) V4 = Anti-dementia (ATC N06D) V5 = Antidepressives (ATC N06A) V6 = Antiparkinson's ATC (N04) V7 = Antidiabetic's (ATC A10) V8 = Psychopharmaca (ATC N05A) V9 = Analgetics (ATC N02A) V10 = Sleepmedication (ATC N05C)

***** (ATC) Anatomical Therapeutic Chemical classification system (https://www.whocc.no/atc_ddd_index/)

Table 2. Cross-table of the predicted test result of the prediction model (DEMO positive or negative) and diagnosis (delirium during admission or no-delirium during admission) 1, 3 and 5 days after DEMO analysis.

.

	Day 1		Day 3		Day 5	
	Delirium during admission	No-delirium during admission	Delirium during admission	No-delirium during admission	Delirium during admission	No-delirium during admission
DEMO Positive	54	71	69	56	82	45
DEMO Negative	8	250	11	247	16	240

Table 3. Estimates of the prevalence, sensitivity, specificity, and likelihood ratios with corresponding 95% confidence intervals 1, 3 and 5 days after DEMO analysis.

	Day 1			Day 3			Day 5		
	Estimated value	95% confidence interval		Estimated value	95% confidence interval		Estimated value	95% confidence interval	
		Lower limit	Upper limit		Lower limit	Upper limit		Lower limit	Upper limit
Prevalence	0.162 (16.2%)	0.127	0.204	0.209 (20.9%)	0.170	0.254	0.256 (25.6%)	0.213	0.303
Sensitivity	0.871 (87.1%)	0.756	0.939	0.863 (86.3%)	0.763	0.926	0.837 (83.7%)	0.745	0.901
Specificity	0.779 (77.9%)	0.729	0.822	0.815 (81.5%)	0.766	0.856	0.842 (84.2%)	0.793	0.881
+LR	3.934	3.140	4.939	4.667	3.627	6.005	5.299	3.997	7.026
-LR	0.166	0.087	0.317	0.169	0.097	0.292	0.194	0.124	0.304

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5	
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	4-5	
Bias	9	Describe any efforts to address potential sources of bias	-	
Study size	10	Explain how the study size was arrived at	4	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	Table 2
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	5-6
		(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	Table 3
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2
		(*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	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
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	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-7
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
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	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Validation of an automated delirium prediction model (DEMO Delirium Model): an observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016654.R3
Article Type:	Research
Date Submitted by the Author:	25-Aug-2017
Complete List of Authors:	Mestres Gonzalvo, Carlota; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology; Elkerliek Ziekenhuis, Clinical Pharmacy de Wit, Hugo; Zuyderland Medisch Centrum Heerlen, Clinical Pharmacy, Pharmacology and Toxicology; Canisius Wilhelmina Ziekenhuis, Clinical Pharmacy van Oijen, Brigit; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Debben, Debbie; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Hurkens, Kim; Zuyderland Medisch Centrum Heerlen, Geriatric Medicine, Department of Internal Medicine Mulder, Wubbo; Maastricht Universitair Medisch Centrum+, Internal Medicine Janknegt, Rob; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Schols, Jos; Maastricht University, Department of General Practice, School for Public Health and Primary Care (CAPHRI) Verhey, Frans; Maastricht University Faculty of Health Medicine and Life Sciences, Psychiatry and Neuropsychology, Alzheimer Centrum Limburg / School for Mental Health and Neurosciences Winkens, Bjorn; Maastricht University, van der Kuy, Hugo; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology; Erasmus MC, Hospital Pharmacy
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Mental health
Keywords:	GERIATRIC MEDICINE, Delirium & cognitive disorders < PSYCHIATRY, PSYCHIATRY

Validation of an automated delirium prediction model (DEMO Delirium Model):
an observational study

C Mestres Gonzalvo (hospital pharmacist)[1,2], HAJM de Wit (hospital pharmacist)[1], BPC van Oijen (hospital pharmacist)[1], D Deben (hospital pharmacist in training)[1], KPGM Hurkens (internist geriatrician)[3], WJ Mulder (internist geriatrician)[4], R Janknegt (hospital pharmacist)[1], JMGA Schols (Professor of Old Age Medicine)[5], FR Verhey (Professor of Geriatric Psychiatry)[6], B Winkens (statistician)[7], PHM van der Kuy (clinical pharmacologist)[1,8]

[1]Department of Clinical Pharmacy, Pharmacology and Toxicology, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen, The Netherlands.
[2]Department of Clinical Pharmacy, Elkerliek Hospital, Wesselmanlaan 25, 5707 HA Helmond, The Netherlands.
[3]Section of Geriatric Medicine, Department of Internal Medicine, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen The Netherlands.
[4]Department of Internal Medicine, Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands.
[5]Department of Family Medicine and Department of Health Services Research, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[6]Department of Psychiatry and Neuropsychology, Alzheimer Centrum Limburg/School for Mental Health and Neurosciences, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[7]Department of Methodology and Statistics, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyeplein 1, 6229 HA Maastricht, The Netherlands.
[8]Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands

Submitting and corresponding author:
Carlota Mestres Gonzalvo
Department of Clinical Pharmacy, Pharmacology and Toxicology
Zuyderland Medical Centre
Dr H van der Hoffplein 1
6162 BG Sittard-Geleen
Phone: +31-88-4597708
E-mail: c.mestresgonzalvo@zuyderland.nl

ABSTRACT

Objectives: Delirium is an under-diagnosed, severe, and costly disorder, and 30-40% of cases can be prevented. A fully automated model to predict delirium (DEMO) in older people has been developed, and the objective of this study is to validate the model in a hospital setting.

Setting: Secondary care, one hospital with two locations

Design: Observational study

Participants: The study included 450 randomly selected patients over 60 years of age admitted to Zuyderland Medical Centre. Patients who presented with delirium upon admission were excluded.

Primary outcome measures: Development of delirium through chart review.

Results: A total of 383 patients were included in this study. The analysis was performed for delirium within 1, 3 and 5 days after a DEMO score was obtained. Sensitivity was 87.1% (CI: 0.756 to 0.939), 84.2% (CI: 0.732 to 0.915), and 82.7% (0.734 to 0.893) for 1, 3, and 5 days, respectively, after obtaining the DEMO score. Specificity was 77.9% (0.729 to 0.882), 81.5% (0.766 to 0.856) and 84.5% (0.797 to 0.884) for 1, 3, and 5 days, respectively, after obtaining the DEMO score.

Conclusion: DEMO is a satisfactory prediction model but needs further prospective validation with in-person delirium confirmation. In the future, DEMO will be applied in clinical practice so that physicians will be aware of when a patient is at an increased risk of developing delirium, which will facilitate earlier recognition and diagnosis, and thus will allow the implementation of prevention measures.

Strengths and limitations of this study

- A high risk of delirium can be predicted electronically by using DEMO (DElirium MOdel) with reasonably good sensitivity and specificity.
- DEMO can be applied in clinical practice to facilitate earlier recognition and diagnosis of delirium.
- Important factors that could predict delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because these data are not yet electronically available.

INTRODUCTION

A delirium or acute confused state is a transient attention and cognition disorder that develops over a short period of time and occurs mainly in hospitalised patients and people aged 60 years and over. Delirium is an under-diagnosed, severe (increased mortality), costly and often preventable disorder [1-3]. Its severity and symptoms can vary considerably, but the main features are impaired cognitive and sensory functions, reduced consciousness, and diminished attention. In addition, it is often accompanied by problems with psychomotor activity, the circadian rhythm, and emotions.

The prevalence and incidence of delirium in the general population differ widely depending on the setting. The overall prevalence in the community is estimated to be 1-2%. In a hospital setting, this prevalence increases to 10-31% at the time of hospital admission and 3-29% during hospitalisation. The incidence increases up to 87% when more specialised populations, such as the elderly and people in postoperative, intensive care and/or palliative care, are considered [4-11]. In 30-40% of cases, delirium is preventable, which, along with its associated high costs (ranging from US$164 billion to US$182 billion per year), makes it a perfect target for interventions by healthcare professionals [1, 4, 12-15]. As a result, a great number of screening tools have been developed and are widely used to detect the early onset of delirium, which can in turn allow treatment measures to be introduced in a timely manner [16-21]. These tools help healthcare professionals to establish and quantify symptoms associated with delirium [19-23]. Once the diagnosis has been established, the underlying medical condition can be targeted, and delirium can be managed appropriately.

There is no effective treatment for delirium [24, 25]. Preventing delirium is by far a more effective strategy to improve patient outcomes [1, 4, 26-29]. Risk models have been used to identify patients at higher risk for delirium development because these patients would most likely benefit from delirium prevention. These models are based on manual evaluation of individual risk factors and may be difficult to implement, so automated models are preferable and more feasible [30-34].

Screening instrument

A fully automated model to predict delirium in older people (over 60 years) was developed at Zuyderland Medical Centre. This DElirium MOdel (DEMO) uses only electronically available data to predict the occurrence of delirium. The predictive variables include age; polypharmacy; and the use of anti-dementia drugs, antidepressants, anti-Parkinson's agents, anti-diabetic drugs, analgesia and/or sleeping tablets (see Table 1). This model can be applied hospital-wide and has an area under receiver operating characteristic (AUROC: measure for model prediction quality) value of 0.770 (95% CI 0736-0804) with a sensitivity of 78.2% and a specificity of 63.7%, when 14.1% is used as a cut-off value for the predicted probability of developing delirium. DEMO was developed retrospectively but has not yet been validated [4].

Therefore, the objective of this study is to validate DEMO in a hospital setting. To do so, the system's accuracy (main study parameter), i.e., sensitivity (proportion of delirium patients who test positive) and specificity (proportion of non-delirium patients who test negative), will be calculated. In addition to

these parameters, the positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+, LR-) with their 95% CI will be computed.

METHODS

This is an observational study of the ability of DEMO to predict delirium in an elderly hospital population. It was conducted in Zuyderland Medical Centre (locations Sittard and Heerlen) in the period from January 2016 to October 2016. The medical ethics committee METC Z (Medisch Ethische Toetsings Commissie van Zuyderland en Zuyd Hogeschool, Zuyderland Medical Centre, Heerlen) approved this study.

DEMO involves a daily analysis of all hospitalised patients ≥ 60 years of age at the different wards and predicts whether a patient is at risk of developing delirium in a 24-hour post-analysis period. The EPR (Electronic Patient Record) was accessed at a later date to check for delirium diagnosis. In this study, DEMO was calculated prospectively, but the outcome was ascertained by chart review retrospectively.

Although delirium diagnosis was determined by chart review, delirium documentation in our hospital is robust. At admission, patients are routinely screened for delirium, both in the emergency department and in the ward. The first screening is performed by a checklist (IGZ Inspectie voor de Gezondheidszorg = Dutch Healthcare Inspectorate, VMS Veiligheidsmanagementsysteem = Safety Management System, and Dutch guideline for delirium) [35, 36]. This checklist consists of 3 questions: does the patient need help with self-care?, has the patients previously suffered a delirium?, does the patients suffer from memory disorders? When one of the questions is positively answered, the patient is at risk of deleloping delirium; in this case the DOSS (Delirium Observation Screening Scale) method [20] is used to evaluate whether a patient has delirium. The DOSS method is a validated method used by nurses to screen for delirium. Its sensitivity ranges from 89-100% and its specificity ranges from 88 to 96.6% [20, 37, 38]

Patients over 60 years who were admitted to Zuyderland were eligible for enrolment. From all patients admitted between 31-12-2015 and 31-10-2016, 450 patients were randomly selected (using https://www.randomlists.com/team-generator) and their charts extracted for review. Patients who, based on chart review, presented with delirium upon admission were then excluded (Figure 1).

A search in the EPR was performed according to patient and date by using the following search terms: "delirium", "delirious", “agitation”, “agitated”, “confused”, “confusion”, “restlessness”, “disturbed”, “disorientation”, “disoriented”, “apathy”, “hallucination”, “mistrust”, “haloperidol”, and “delirium prevention measures”. These search terms were discussed with an internist geriatrician, a professor of geriatric medicine and a professor of geriatric psychiatry.

The search was performed by first identifying where the different words appeared in the EPR, and then, if any of these words appeared, the whole EPR during the admission period was read and

interpreted by two authors (KH (internist geriatrician) and CMG (hospital pharmacist)) to determine whether it was truly a delirium diagnosis. All notes were reviewed, including notes by physicians, nurses, physiotherapists, and speech therapists. During the study, treating healthcare professionals (physicians, nurses etc.) were blinded to DEMO scores in order to avoid bias. If a diagnosis of delirium could not be established for a patient as a result of insufficient information in the chart, this patient was excluded from the analysis. The date of delirium onset was determined by chart review.

Delirium diagnosis based on chart review was then compared with the risk score from DEMO. The DEMO was dichotomized into two groups: high risk ≥ 14.1% [4], and low risk <14.1% for this analysis. A two-by-two table was then constructed to calculate True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN) rates.

The predictive value of DEMO was determined for delirium developing within 1, 3, and 5 days after the DEMO score was
calculated. It had been developed to predict delirium within the next 24 hours, but here we wished to also investigate whether its predictive value could be extended to three or five days.

In the study wherein the DEMO was developed, an incidence rate of 17.4% was used [4]. Given the assumption of the same sensitivity of 0.75 (75%), we calculated that 33 delirium patients were needed based upon the requirement that the lower limit of 95% CI would be at least 60% (width of 95%CI ≤ 0.30 (30%)). With regard to the specificity, the number of non-delirium patients would be much larger than the number of delirium patients, and hence, the width of the 95% confidence interval (CI) for specificity would be smaller than 0.30.

It was assumed that at least 332 patients would be needed to identify 33 delirium patients. Taking into account the exclusion criteria and the possibility of a smaller percentage of patients who would develop delirium, a sufficient number of patients were screened to obtain 33 delirium patients (i.e., 450 patients).

The sensitivity, specificity, PPV, NPV, LR+, LR- with corresponding 95% confidence intervals were calculated with the use of an online calculator (http://vassarstats.net/clin1.html).

The differences in PPV and NPV over time were tested using McNemar's test. The differences in age and gender between delirium and non-delirium groups were tested by using the independent-samples t-test and chi-square test, respectively. IBM SPSS statistics for Windows (version 23.0) was used to perform these tests. A two-sided p-value smaller than or equal to 0.05 was considered statistically significant.

RESULTS

The study lasted eight months, and a total of 383 patients were included (Figure 1 - supplementary figure). The results of the diagnostic test (TP/FP/FN/TN) for 1, 3 and 5 days after DEMO analysis are shown in Table 2. The analysis, including prevalence estimates, sensitivity, specificity, PPV, NPV, and likelihood ratios, is presented in Table 3. Although sensitivity decreased and specificity increased if the period increased from 1 day to 3 or 5 days after DEMO score was obtained, all values were rather high (sensitivity ≥ 0.827, specificity ≥ 0.779). PPV was statistically different $p < 0.001$ for all three comparisons (1 vs 3 days, 1 vs 5 days, 3 vs 5 days), NPV was not statistically different $p = 0.25$, 0.004, 0.031 for 1 vs 3 days, 1 vs 5 days and 3 vs 5 days, respectively.

Patients who developed delirium within 5 days were significantly older (mean age 83.9 (sd 7.8)) compared to those who did not develop a delirium within 5 days (mean age 73.9 (sd 9.1); $p < 0.001$). There was no significant difference in the percentage of males within the delirium and non-delirium groups (50.0% versus 50.1%, p=0.911).

DISCUSSION AND CONCLUSION

In the current study, a previously developed model for predicting delirium has been validated. DEMO was calculated prospectively, and the outcome was ascertained by chart review retrospectively. Based on the current data and the high sensitivity and specificity, it can be concluded that DEMO is a satisfactory prediction model.

Another strength of DEMO is that it predicts delirium on a daily basis. This is a novel concept, as most delirium prediction rules apply at admission but not daily. Even though it is not clear whether there is a definite advantage to predicting delirium on a daily basis, as this could lead to information overload, it could eventually be something that is tracked along with vital signs and intake/output.

We found sensitivity and specificity rates that were higher than reported in the study of de Wit et al., which may be because his study only checked the patients' medical history for delirium and not the entire EPR. Moreover, de Wit et al. had performed the search merely on the diagnosis of delirium. In the current study, the full EPR during the admission period was taken into account, and a wider set of terms was considered for delirium diagnosis. Furthermore, in the current study, in those cases in which delirium was not clear, these patients were excluded, whereas such patients had been included in the development of the delirium model [4].

The present study does present some limitations. First, the validation of the DElirium MOdel depends on how and when a healthcare professional reports that a patient has developed delirium. It is well known that documentation of delirium is poor since the majority of delirium remains unrecognised by clinical teams [39]. We therefore performed a wider search considering other words that might suggest delirium as delirium diagnosis and read through the whole EPR during the admission period. The number of delirium patients is noticeably higher than originally found, which can be explained by

the search we performed. The DEMO is merely an aid to detect delirium, not a diagnostic tool by itself.

In addition, as mentioned in the study by Inouye et al. [40], using a chart review method has some limitations as it has a 30% false positive rate and thus it is possible that patients with delirium at admission may have been included in the non-delirious cohort due to poor documentation in the chart. Nevertheless, the fact that validated checklists are used to screen for delirium and that the chart is a complete document in which different healthcare professionals note their findings makes the outcome more reliable and strengthens the validity of the present study.
Another limitation of the present study is that this is a single-centre study (two hospital locations) located in the Netherlands and may not be generalisable in other settings.

The DEMO uses only electronically available data. Other important factors that could predict a delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because they were not electronically available. If these data were also made electronically available, the predictive quality of DEMO could be improved [22, 23, 27, 30]. Taking into account that the registration of such factors is becoming increasingly important and mandatory, it is only a matter of time until these important factors can be used in the DEMO [2, 3]. In addition, DEMO already uses an alternative way of identifying cognitive impairment by including medications used for dementia.

The DElirium MOdel is a fully automated satisfactory prediction model that predicts delirium up to 5 days after analysis. The next step is to validate the DEMO in a cohort in which the outcome of delirium would be prospectively assessed in person and to use DEMO for retrospective measurements. In the future, DEMO will be applied to clinical practice so that physicians are alerted when a patient is at increased risk of developing delirium. This will facilitate earlier recognition and diagnosis and, thus, the implementation of prevention measures.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from ABC Company for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

FUNDING

This work was supported by ZonMw (the Netherlands Organisation for Health Research and Development) grant number [113101001]

AUTHORS' CONTRIBUTIONS

All authors have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; They all have been involved in drafting the manuscript and revising it critically for important intellectual content; They all have given final approval of the version to be published; and they all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conception or design of the work

C Mestres Gonzalvo
HAJM de Wit
BPC van Oijen
DS Deben
KPGM Hurkens
WJ Mulder
R Janknegt
JMGA Schols
FR Verhey
B Winkens
PHM van der Kuy

Data collection

C Mestres Gonzalvo
DS Deben
KPGM Hurkens

Data analysis and interpretation

C Mestres Gonzalvo
KPGM Hurkens
FR Verhey
B Winkens
PHM van der Kuy

Drafting the article

C Mestres Gonzalvo

Critical revision of the article

HAJM de Wit
BPC van Oijen
JMGA Schols

FR Verhey
B Winkens
PHM van der Kuy

Final approval of the version to be published

C Mestres Gonzalvo
HAJM de Wit
BPC van Oijen
DS Deben
KPGM Hurkens
WJ Mulder
R Janknegt
JMGA Schols
FR Verhey
B Winkens
PHM van der Kuy

TRANSPARENCY DECLARATION

C. Mestres Gonzalvo affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING

All data is anonymized and will be confidentially handled. Only the investigators have access to the data.
All patient data will be kept for as long as the project is being conducted.

EXCLUSIVE LICENCE

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the publishers.

(http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.doc)

REFERENCES

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-22.
2. Delirium: Diagnosis, prevention and management. NICE guidelines [CG103] Published date: July 2010
3. Delirium for adults Dutch guideline. Richtlijn Delier Volwassenen. Nederlandse Vereniging voor Klinische Geriatrie (NVKG) 2013
4. Hugo AJM de Wit, Bjorn Winkens, Carlota Mestres Gonzalvo, Kim PGM Hurkens, Wubbo J Mulder, Rob Janknegt, Frans R Verhey, Paul-Hugo M van der Kuy, and Jos MGA Schols. The development of an automated ward independent delirium risk prediction model. Int J Clin Pharm (2016) 38:915–923
5. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35(4):350-64.
6. Ryan DJ, O'Regan NA, Caoimh RÓ, et al: Delirium in an adult acute hospital population: predictors, prevalence and detection. BMJ Open 2013; 3(1). http://dx.doi.org/10.1136/bmjopen-2012-001772
7. Inouye SK. Delirium in hospitalized older patients. Clin. Geriatr. Med. 1998;14:745–764.
8. Bruce, A. J., Ritchie, C. W., Blizard, R., Lai, R. & Raven, P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. Int. Psychogeriatr. 19, 197-214 (2007).
9. Girard, T. D. & Ely, E. W. Delirium in the critically ill patient. Handb. Clin. Neurol. 90, 39-56 (2008)
10. Inouye SK. Delirium in older persons. N. Engl. J. Med. 2006;354:1157–1165
11. Pisani, M. A., McNicoll, L. & Inouye, S. K. Cognitive impairment in the intensive care unit. N. Engl. J. Med. 24, 727-737 (2003)
12. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008 Jan 14;168(1):27-32. PubMed PMID: 18195192.
13. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
14. WHO Regional Offi ce for Europe. European hospital morbidity database. Copenhagen: World Health Organization, 2012.
15. Organisation for Economic Co-operation and Development. OECD health data 2012. Paris: Organisation for Economic Co-operation and Development, 2012.
16. Adamis D, Sharma N, Whelan PJ, Macdonald AJ. Delirium scales: a review of current evidence. Aging Ment Health 2010; 14: 543–55.
17. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA 2010; 304: 779–86.
18. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec 15;113(12):941-8. PubMed PMID: 2240918. Epub 1990/12/15.

19.Jin H. Han MD, MSc1,and Eduard E. Vasilevskis. Ultrabrief delirium assessments—are they ready for primetime? DOI: 10.1002/jhm.2478

20.Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pract. 2003 Spring;17(1):31-50. PubMed PMID: 12751884. Epub 2003/05/20.

21.van Velthuijsen EL, et al. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. Int J Geriatr Psychiatry. 2016 Sep;31(9):974-89. doi: 10.1002/gps.4441. Epub 2016 Feb 21.

22.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):249-54. PubMed PMID: 18707947. Epub 2008/08/19.

23.Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord. 1999 Sep-Oct;10(5):393-400. PubMed PMID: 10473946. Epub 1999/09/04.

24.AGS/NIA Delirium Conference Writing Group PC, Faculty: The American Geriatrics Society/National Institute on Aging Bedside-to-Bench Conference: Research Agenda on Delirium in Older Adults. Journal of the American Geriatrics Society 2015, 63(5):843-852.

25.Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM: Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society 2016, 64(4):705-714.

26.Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. Neurotherapeutics. 2012 Jan;9(1):158-75. doi: 10.1007/s13311-011-0102-9.

27.Young J, Leentjens AF, George J, Olofsson B, Gustafson Y. Systematic approaches to the prevention and management of patients with delirium. J Psychosom Res. 2008 Sep;65(3):267-72. PubMed PMID: 18707950.

28.Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. Psychosomatics. 2013 Mar-Apr;54(2):124-31. PubMed PMID: 23380670.

29.Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005 Oct;53(10):1658-66. PubMed PMID: 16181163.

30.Kishi T, et al. J Neurol Neurosurg Psychiatry 2016;87:767–774. doi:10.1136/jnnp-2015-311049

31.van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012;344:e420. PubMed PMID: 22323509. Pubmed Central PMCID: 3276486.

32.Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med. 1993 Sep 15;119(6):474-81. PubMed PMID: 8357112.

33. Carrasco MP, Villarroel L, Andrade M, et al. Development and validation of a delirium predictive score in older people. Age Ageing. 2014;43(3):346-51.
34. Douglas VC, Hessler CS, Dhaliwal G, et al. The AWOL tool: derivation and validation of a delirium prediction rule. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2013;8(9):493-9.)
35. http://www.vmszorg.nl/ (Visited on 20/6/2017)
36. Guideline delirium adults and elderly (Richtlijn delier volwassen en ouderen 2013) http://www.vmszorg.nl/_library/24018/Richtlijn%20Delier%20Volwassenen%20en%20ouderen%202014.pdf
37. van Gemert LA, Schuurmans MJ. The Neecham Confusion Scale and the Delirium Observation Screening Scale: Capacity to discriminate and ease of use in clinical practice. BMC Nursing 2007;6:3.
38. The Delirium Observation Screening scale recognizes delirium early after cardiac surgery Eur J Cardiovasc Nurs. 2009 Oct;8(4):309-14
39. Collins N, Blanchard MR, Tookman A, Sampson EL: Detection of delirium in the acute hospital. Age Ageing 2010, 39(1):131-135.
40. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST, Jr., Leslie DL, Agostini JV: A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. Journal of the American Geriatrics Society 2005, 53(2):312-318.

Table 1. DElirium MOdel and cut-off point

DEMO-score = 1/(1+e-(Linear predictor)) DEMO score > 14.1% → Increased rrisk at delirium DEMO score ≤ 14.1% → No increased risk at delirium
Linear predictor = -8.823 + (0.081*V1) + (0.031*V2) + (0.248*V3) + (1.123*V4) + (0.286*V5) + (1.963*V6) + (0.359*V7) + (1.199*V8) + (0.413*V9) + (0.103*V10) V1 = Age (years) V2 = Polypharmacy (number of drugs) V3 = Anxiolytics (ATC N05B) V4 = Anti-dementia (ATC N06D) V5 = Antidepressives (ATC N06A) V6 = Antiparkinson's ATC (N04) V7 = Antidiabetic's (ATC A10) V8 = Psychopharmaca (ATC N05A) V9 = Analgetics (ATC N02A) V10 = Sleepmedication (ATC N05C)

* (ATC) Anatomical Therapeutic Chemical classification system (https://www.whocc.no/atc_ddd_index/)

Table 2. Test results of the prediction model (DEMO positive or negative) and diagnosis (delirium during admission or no-delirium during admission) within 1, 3 and 5 days after DEMO analysis.

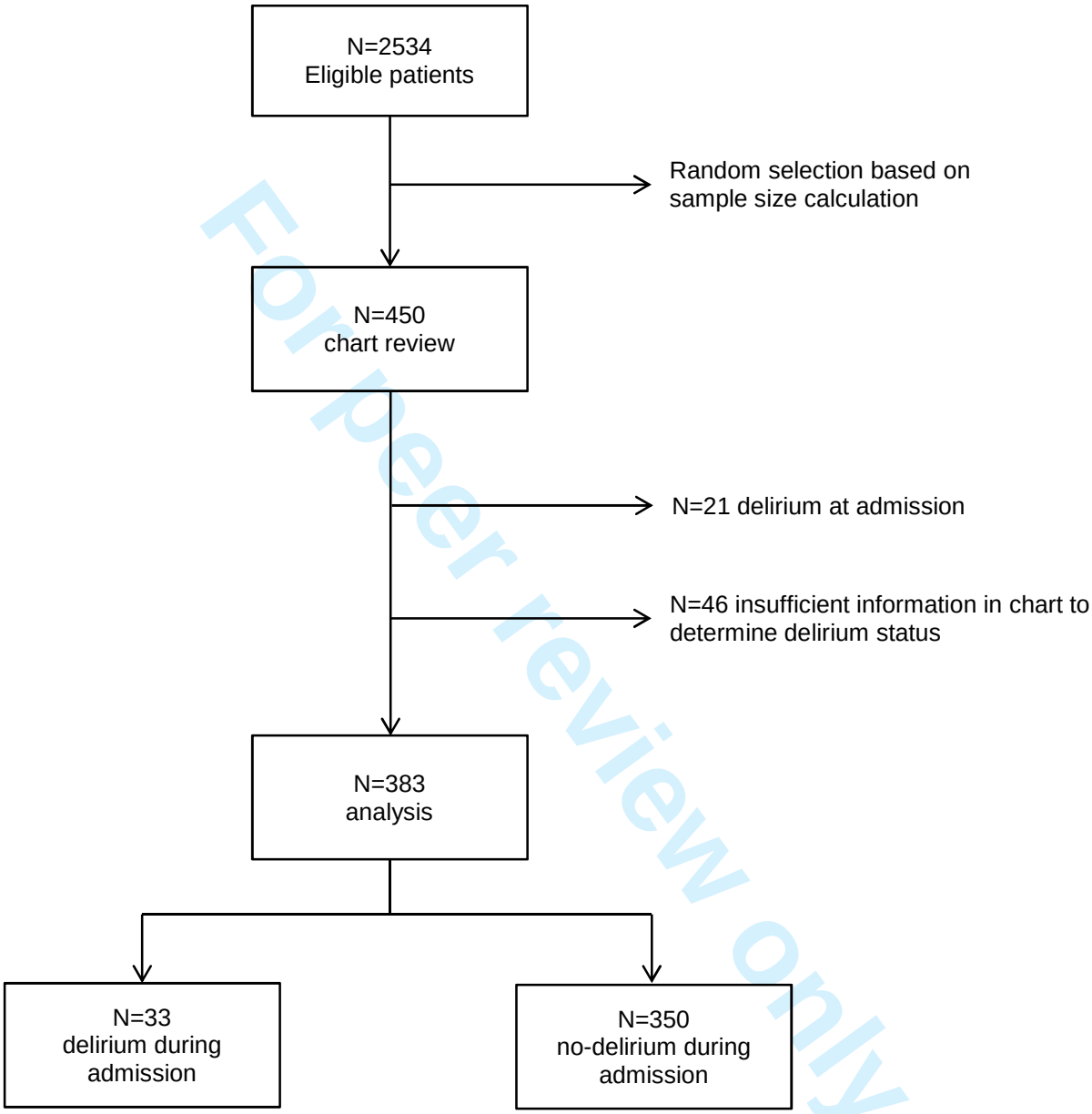
	Delirium within 1 day after DEMO	No-delirium within 1 day after DEMO	Delirium within 3 days after DEMO	No-delirium within 3 days after DEMO	Delirium within 5 days after DEMO	No-delirium within 5 days after DEMO
DEMO Positive	54	71	69	56	81	44
DEMO Negative	8	250	11	247	17	241

Table 3. Estimates of the prevalence, sensitivity, specificity, PPV, NPV, and likelihood ratios with corresponding 95% confidence intervals 1, 3 and 5 days after DEMO analysis.

	Day 1 after DEMO analysis			Day 3 after DEMO analysis			Day 5 after DEMO analysis		
	Estimated value	95% confidence interval		Estimated value	95% confidence interval		Estimated value	95% confidence interval	
		Lower limit	Upper limit		Lower limit	Upper limit		Lower limit	Upper limit
Prevalence	0.162 (16.2%)	0.127	0.204	0.188 (18.8%)	0.150	0.221	0.256 (25.6%)	0.213	0.303
Sensitivity	0.871 (87.1%)	0.756	0.939	0.842 (84.2%)	0.732	0.915	0.827 (82.7%)	0.734	0.893
	0.779 (77.9%)	0.729	0.822	0.815 (81.5%)	0.766	0.856	0.845 (84.5%)	0.797	0.884
PPV	0.432 (43.20%)*	0.345	0.524	0.513 (51.3%)*	0.419	0.607	0.648 (64.8%)*	0.557	0.730
NPV	0.969 (96.90%)	0.938	0.986	0.957 (95.7%)	0.922	0.977	0.934 (93.4%)	0.895	0.960
LR +	3.938	3.140	4.939	4.560	3.526	5.898	5.354	4.020	7.129
LR -	0.166	0.087	0.317	0.193	0.112	0.332	0.205	0.133	0.316

*PPV: Statistically different $p < 0.001$ for all three comparisons (1 vs 3 days, 1 vs 5 days, 3 vs 5 days)

Figure 1. Flow diagram inclusion



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5	
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	4-5	
Bias	9	Describe any efforts to address potential sources of bias	-	
Study size	10	Explain how the study size was arrived at	4	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	Table 2
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	5-6
		(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	Table 3
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2
		(*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	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
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	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-7
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
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	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Validation of an automated delirium prediction model (DEMO Delirium Model): an observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016654.R4
Article Type:	Research
Date Submitted by the Author:	06-Oct-2017
Complete List of Authors:	Mestres Gonzalvo, Carlota; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology; Elkerliek Ziekenhuis, Clinical Pharmacy de Wit, Hugo; Zuyderland Medisch Centrum Heerlen, Clinical Pharmacy, Pharmacology and Toxicology; Canisius Wilhelmina Ziekenhuis, Clinical Pharmacy van Oijen, Brigit; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Debben, Debbie; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Hurkens, Kim; Zuyderland Medisch Centrum Heerlen, Geriatric Medicine, Department of Internal Medicine Mulder, Wubbo; Maastricht Universitair Medisch Centrum+, Internal Medicine Janknegt, Rob; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology Schols, Jos; Maastricht University, Department of General Practice, School for Public Health and Primary Care (CAPHRI) Verhey, Frans; Maastricht University Faculty of Health Medicine and Life Sciences, Psychiatry and Neuropsychology, Alzheimer Centrum Limburg / School for Mental Health and Neurosciences Winkens, Bjorn; Maastricht University, van der Kuy, Hugo; Zuyderland, Clinical Pharmacy, Pharmacology and Toxicology; Erasmus MC, Hospital Pharmacy
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Mental health
Keywords:	GERIATRIC MEDICINE, Delirium & cognitive disorders < PSYCHIATRY, PSYCHIATRY

Validation of an automated delirium prediction model (DEMO Delirium Model):
an observational study

C Mestres Gonzalvo (hospital pharmacist)[1,2], HAJM de Wit (hospital pharmacist)[1], BPC van Oijen (hospital pharmacist)[1], D Deben (hospital pharmacist in training)[1], KPGM Hurkens (internist geriatrician)[3], WJ Mulder (internist geriatrician)[4], R Janknegt (hospital pharmacist)[1], JMGA Schols (Professor of Old Age Medicine)[5], FR Verhey (Professor of Geriatric Psychiatry)[6], B Winkens (statistician)[7], PHM van der Kuy (clinical pharmacologist)[1,8]

[1]Department of Clinical Pharmacy, Pharmacology and Toxicology, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen, The Netherlands.
[2]Department of Clinical Pharmacy, Elkerliek Hospital, Wesselmanlaan 25, 5707 HA Helmond, The Netherlands.
[3]Section of Geriatric Medicine, Department of Internal Medicine, Zuyderland Medical Centre, Dr. H van der Hoffplein 1, 6162 BG, Sittard-Geleen The Netherlands.
[4]Department of Internal Medicine, Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands.
[5]Department of Family Medicine and Department of Health Services Research, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[6]Department of Psychiatry and Neuropsychology, Alzheimer Centrum Limburg/School for Mental Health and Neurosciences, Maastricht University, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands.
[7]Department of Methodology and Statistics, CAPHRI-School for Public Health and Primary Care, Maastricht University, P. Debyeplein 1, 6229 HA Maastricht, The Netherlands.
[8]Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands

Submitting and corresponding author:
Carlota Mestres Gonzalvo
Department of Clinical Pharmacy, Pharmacology and Toxicology
Zuyderland Medical Centre
Dr H van der Hoffplein 1
6162 BG Sittard-Geleen
Phone: +31-88-4597708
E-mail: c.mestresgonzalvo@zuyderland.nl

ABSTRACT

Objectives: Delirium is an under-diagnosed, severe, and costly disorder, and 30-40% of cases can be prevented. A fully automated model to predict delirium (DEMO) in older people has been developed, and the objective of this study is to validate the model in a hospital setting.

Setting: Secondary care, one hospital with two locations

Design: Observational study

Participants: The study included 450 randomly selected patients over 60 years of age admitted to Zuyderland Medical Centre. Patients who presented with delirium upon admission were excluded.

Primary outcome measures: Development of delirium through chart review.

Results: A total of 383 patients were included in this study. The analysis was performed for delirium within 1, 3 and 5 days after a DEMO score was obtained. Sensitivity was 87.1% (CI: 0.756 to 0.939), 84.2% (CI: 0.732 to 0.915), and 82.7% (0.734 to 0.893) for 1, 3, and 5 days, respectively, after obtaining the DEMO score. Specificity was 77.9% (0.729 to 0.882), 81.5% (0.766 to 0.856) and 84.5% (0.797 to 0.884) for 1, 3, and 5 days, respectively, after obtaining the DEMO score.

Conclusion: DEMO is a satisfactory prediction model but needs further prospective validation with in-person delirium confirmation. In the future, DEMO will be applied in clinical practice so that physicians will be aware of when a patient is at an increased risk of developing delirium, which will facilitate earlier recognition and diagnosis, and thus will allow the implementation of prevention measures.

Strengths and limitations of this study

- A high risk of delirium can be predicted electronically by using DEMO (DElirium MOdel) with reasonably good sensitivity and specificity.
- DEMO can be applied in clinical practice to facilitate earlier recognition and diagnosis of delirium.
- Important factors that could predict delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because these data are not yet electronically available.

INTRODUCTION

A delirium or acute confused state is a transient attention and cognition disorder that develops over a short period of time and occurs mainly in hospitalised patients and people aged 60 years and over. Delirium is an under-diagnosed, severe (increased mortality), costly and often preventable disorder [1-3]. Its severity and symptoms can vary considerably, but the main features are impaired cognitive and sensory functions, reduced consciousness, and diminished attention. In addition, it is often accompanied by problems with psychomotor activity, the circadian rhythm, and emotions.

The prevalence and incidence of delirium in the general population differ widely depending on the setting. The overall prevalence in the community is estimated to be 1-2%. In a hospital setting, this prevalence increases to 10-31% at the time of hospital admission and 3-29% during hospitalisation. The incidence increases up to 87% when more specialised populations, such as the elderly and people in postoperative, intensive care and/or palliative care, are considered [4-11]. In 30-40% of cases, delirium is preventable, which, along with its associated high costs (ranging from US$164 billion to US$182 billion per year), makes it a perfect target for interventions by healthcare professionals [1, 4, 12-15]. As a result, a great number of screening tools have been developed and are widely used to detect the early onset of delirium, which can in turn allow treatment measures to be introduced in a timely manner [16-21]. These tools help healthcare professionals to establish and quantify symptoms associated with delirium [19-23]. Once the diagnosis has been established, the underlying medical condition can be targeted, and delirium can be managed appropriately.

There is no effective treatment for delirium [24, 25]. Preventing delirium is by far a more effective strategy to improve patient outcomes [1, 4, 26-29]. Risk models have been used to identify patients at higher risk for delirium development because these patients would most likely benefit from delirium prevention. These models are based on manual evaluation of individual risk factors and may be difficult to implement, so automated models are preferable and more feasible [30-34].

Screening instrument

A fully automated model to predict delirium in older people (over 60 years) was developed at Zuyderland Medical Centre. This DElirium MOdel (DEMO) uses only electronically available data to predict the occurrence of delirium. The predictive variables include age; polypharmacy; and the use of anti-dementia drugs, antidepressants, anti-Parkinson's agents, anti-diabetic drugs, analgesia and/or sleeping tablets (see Table 1). This model can be applied hospital-wide and has an area under receiver operating characteristic (AUROC: measure for model prediction quality) value of 0.770 (95% CI 0736-0804) with a sensitivity of 78.2% and a specificity of 63.7%, when 14.1% is used as a cut-off value for the predicted probability of developing delirium. DEMO was developed retrospectively but has not yet been validated [4].

Therefore, the objective of this study is to validate DEMO in a hospital setting. To do so, the system's accuracy (main study parameter), i.e., sensitivity (proportion of delirium patients who test positive)

and specificity (proportion of non-delirium patients who test negative), will be calculated. In addition to these parameters, the positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+, LR-) with their 95% CI will be computed.

METHODS

This is an observational study of the ability of DEMO to predict delirium in an elderly hospital population. It was conducted in Zuyderland Medical Centre (locations Sittard and Heerlen) in the period from January 2016 to October 2016. The medical ethics committee METC Z (Medisch Ethische Toetsings Commissie van Zuyderland en Zuyd Hogeschool, Zuyderland Medical Centre, Heerlen) approved this study.

DEMO involves a daily analysis of all hospitalised patients ≥ 60 years of age at the different wards and predicts whether a patient is at risk of developing delirium in a 24-hour post-analysis period. The EPR (Electronic Patient Record) was accessed at a later date to check for delirium diagnosis. In this study, DEMO was calculated prospectively, but the outcome was ascertained by chart review retrospectively.

Although delirium diagnosis was determined by chart review, delirium documentation in our hospital is robust. At admission, patients are routinely screened for delirium, both in the emergency department and in the ward. The first screening is performed by a checklist (IGZ Inspectie voor de Gezondheidszorg = Dutch Healthcare Inspectorate, VMS Veiligheidsmanagementsysteem = Safety Management System, and Dutch guideline for delirium) [35, 36]. This checklist consists of 3 questions: does the patient need help with self-care?, has the patients previously suffered a delirium?, does the patients suffer from memory disorders? When one of the questions is positively answered, the patient is at risk of developing delirium; in this case the DOSS (Delirium Observation Screening Scale) method [20] is used to evaluate whether a patient has delirium and it is subsequently noted in the chart.

Patients over 60 years who were admitted to Zuyderland were eligible for enrolment. From all patients admitted between 31-12-2015 and 31-10-2016, 450 patients were randomly selected (using https://www.randomlists.com/team-generator) and their charts extracted for review. Patients who, based on chart review, presented with delirium upon admission were then excluded (Figure 1).

A search in the EPR was performed according to patient and date by using the following search terms: "delirium", "delirious", “agitation”, “agitated”, “confused”, “confusion”, “restlessness”, “disturbed”, “disorientation”, “disoriented”, “apathy”, “hallucination”, “mistrust”, “haloperidol”, and “delirium prevention measures”. These search terms were discussed with an internist geriatrician, a professor of geriatric medicine and a professor of geriatric psychiatry.
The search was performed by first identifying where the different words appeared in the EPR, and then, if any of these words appeared, the whole EPR during the admission period was read and

interpreted by two authors (KH (internist geriatrician) and CMG (hospital pharmacist)) to determine whether it was truly a delirium diagnosis. All notes were reviewed, including notes by physicians, nurses, physiotherapists, and speech therapists. During the study, treating healthcare professionals (physicians, nurses etc.) were blinded to DEMO scores in order to avoid bias. If a diagnosis of delirium could not be established for a patient as a result of insufficient information in the chart, this patient was excluded from the analysis. The date of delirium onset was determined by chart review.

Delirium diagnosis based on chart review was then compared with the risk score from DEMO. The DEMO was dichotomized into two groups: high risk ≥ 14.1% [4], and low risk <14.1% for this analysis. A two-by-two table was then constructed to calculate True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN) rates.

The predictive value of DEMO was determined for delirium developing within 1, 3, and 5 days after the DEMO score was
calculated. It had been developed to predict delirium within the next 24 hours, but here we wished to also investigate whether its predictive value could be extended to three or five days.

In the study wherein the DEMO was developed, an incidence rate of 17.4% was used [4]. Given the assumption of the same sensitivity of 0.75 (75%), we calculated that 33 delirium patients were needed based upon the requirement that the lower limit of 95% CI would be at least 60% (width of 95%CI ≤ 0.30 (30%)). With regard to the specificity, the number of non-delirium patients would be much larger than the number of delirium patients, and hence, the width of the 95% confidence interval (CI) for specificity would be smaller than 0.30.

It was assumed that at least 332 patients would be needed to identify 33 delirium patients. Taking into account the exclusion criteria and the possibility of a smaller percentage of patients who would develop delirium, a sufficient number of patients were screened to obtain 33 delirium patients (i.e., 450 patients).

The sensitivity, specificity, PPV, NPV, LR+, LR- with corresponding 95% confidence intervals were calculated with the use of an online calculator (http://vassarstats.net/clin1.html).

The differences in PPV and NPV over time were tested using McNemar's test. The differences in age and gender between delirium and non-delirium groups were tested by using the independent-samples t-test and chi-square test, respectively. IBM SPSS statistics for Windows (version 23.0) was used to perform these tests. A two-sided p-value smaller than or equal to 0.05 was considered statistically significant.

RESULTS

The study lasted eight months, for 450 patients chart review was undergone. Finally a total of 383 patients were included, as 21 patients presented with delirium at admission, and for 46 patients there was insufficient information to determine delirium status (Figure 1 - supplementary figure). The results of the diagnostic test (TP/FP/FN/TN) for 1, 3 and 5 days after DEMO analysis are shown in Table 2. The analysis, including prevalence estimates, sensitivity, specificity, PPV, NPV, and likelihood ratios, is presented in Table 3. Although sensitivity decreased and specificity increased if the period increased from 1 day to 3 or 5 days after DEMO score was obtained, all values were rather high (sensitivity ≥ 0.827, specificity ≥ 0.779). PPV was statistically different $p < 0.001$ for all three comparisons (1 vs 3 days, 1 vs 5 days, 3 vs 5 days), NPV was not statistically different $p = 0.25$, 0.004, 0.031 for 1 vs 3 days, 1 vs 5 days and 3 vs 5 days, respectively.

Patients who developed delirium within 5 days were significantly older (mean age 83.9 (sd 7.8)) compared to those who did not develop a delirium within 5 days (mean age 73.9 (sd 9.1); $p < 0.001$). There was no significant difference in the percentage of males within the delirium and non-delirium groups (50.0% versus 50.1%, p=0.911).

DISCUSSION AND CONCLUSION

In the current study, a previously developed model for predicting delirium has been validated. DEMO was calculated prospectively, and the outcome was ascertained by chart review retrospectively. Based on the current data and the high sensitivity and specificity, it can be concluded that DEMO is a satisfactory prediction model.

Another strength of DEMO is that it predicts delirium within 5 days post-analysis on a daily basis.. This is a novel concept, as most delirium prediction rules apply at admission but not daily. Even though it is not clear whether there is a definite advantage to predicting delirium on a daily basis, as this could lead to information overload, it could eventually be something that is tracked along with vital signs and intake/output.

We found sensitivity and specificity rates that were higher than reported in the study of de Wit et al., which may be because his study only checked the patients' medical history for delirium and not the entire EPR. Moreover, de Wit et al. had performed the search merely on the diagnosis of delirium. In the current study, the full EPR during the admission period was taken into account, and a wider set of terms was considered for delirium diagnosis. Furthermore, in the current study, in those cases in which delirium was not clear, these patients were excluded, whereas such patients had been included in the development of the delirium model [4].

The present study does present some limitations. First, the validation of the DElirium MOdel depends on how and when a healthcare professional reports that a patient has developed delirium. It is well known that documentation of delirium is poor since the majority of delirium remains unrecognised by

clinical teams [37]. We therefore performed a wider search considering other words that might suggest delirium as delirium diagnosis and read through the whole EPR during the admission period. The number of delirium patients is noticeably higher than originally found, which can be explained by the search we performed. The DEMO is merely an aid to detect delirium, not a diagnostic tool by itself. Furthermore, for 46 patients there was insufficient information in the chart to determine delirium status, which could influence the generalisability of the present study.

In addition, as mentioned in the study by Inouye et al. [38], using a chart review method has some limitations as it has a 30% false positive rate and thus it is possible that patients with delirium at admission may have been included in the non-delirious cohort due to poor documentation in the chart. Furthermore, the checklist used to screen the patients is a non-validated tool. Nevertheless, after that first check, the DOSS is used. The DOSS method is a validated method used by nurses to screen for delirium. Its sensitivity ranges from 89-100% and its specificity ranges from 88 to 96.6% [20, 39, 40]. The DOSS scores and its conclusion (delirium/non-delirium) are recorded in the chart. In that way, and taking into account that the chart is a complete document in which different healthcare professionals note their findings, makes the outcome more reliable and strengthens the validity of the present study.
Another limitation of the present study is that this is a single-centre study (two hospital locations) located in the Netherlands and may not be generalisable in other settings.

The DEMO uses only electronically available data. Other important factors that could predict a delirium (previous delirium, cognitive impairment, severity of disease, visual impairment, etc.) are not included in this model because they were not electronically available. If these data were also made electronically available, the predictive quality of DEMO could be improved [22, 23, 27, 30]. Taking into account that the registration of such factors is becoming increasingly important and mandatory, it is only a matter of time until these important factors can be used in the DEMO [2, 3]. In addition, DEMO already uses an alternative way of identifying cognitive impairment by including medications used for dementia.

The DElirium MOdel is a fully automated satisfactory prediction model that predicts delirium up to 5 days after analysis. The next step is to validate the DEMO in a cohort in which the outcome of delirium would be prospectively assessed in person and to use DEMO for retrospective measurements. In the future, DEMO will be applied to clinical practice so that physicians are alerted when a patient is at increased risk of developing delirium. This will facilitate earlier recognition and diagnosis and, thus, the implementation of prevention measures.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from ABC Company for the submitted work; no financial

relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

FUNDING

This work was supported by ZonMw (the Netherlands Organisation for Health Research and Development) grant number [113101001]

AUTHORS' CONTRIBUTIONS

All authors have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; They all have been involved in drafting the manuscript and revising it critically for important intellectual content; They all have given final approval of the version to be published; and they all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conception or design of the work

C Mestres Gonzalvo
HAJM de Wit
BPC van Oijen
DS Deben
KPGM Hurkens
WJ Mulder
R Janknegt
JMGA Schols
FR Verhey
B Winkens
PHM van der Kuy

Data collection

C Mestres Gonzalvo
DS Deben
KPGM Hurkens

Data analysis and interpretation

C Mestres Gonzalvo
KPGM Hurkens
FR Verhey
B Winkens
PHM van der Kuy

Drafting the article

C Mestres Gonzalvo

Critical revision of the article

HAJM de Wit

BPC van Oijen

JMGA Schols

FR Verhey

B Winkens

PHM van der Kuy

Final approval of the version to be published

C Mestres Gonzalvo

HAJM de Wit

BPC van Oijen

DS Deben

KPGM Hurkens

WJ Mulder

R Janknegt

JMGA Schols

FR Verhey

B Winkens

PHM van der Kuy

TRANSPARENCY DECLARATION

C. Mestres Gonzalvo affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING

All data is anonymized and will be confidentially handled. Only the investigators have access to the data.

All patient data will be kept for as long as the project is being conducted.

EXCLUSIVE LICENCE

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the publishers.

(http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.doc)

REFERENCES

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-22.
2. Delirium: Diagnosis, prevention and management. NICE guidelines [CG103] Published date: July 2010
3. Delirium for adults Dutch guideline. Richtlijn Delier Volwassenen. Nederlandse Vereniging voor Klinische Geriatrie (NVKG) 2013
4. Hugo AJM de Wit, Bjorn Winkens, Carlota Mestres Gonzalvo, Kim PGM Hurkens, Wubbo J Mulder, Rob Janknegt, Frans R Verhey, Paul-Hugo M van der Kuy, and Jos MGA Schols. The development of an automated ward independent delirium risk prediction model. Int J Clin Pharm (2016) 38:915–923
5. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35(4):350-64.
6. Ryan DJ, O'Regan NA, Caoimh RÓ, et al: Delirium in an adult acute hospital population: predictors, prevalence and detection. BMJ Open 2013; 3(1). http://dx.doi.org/10.1136/bmjopen-2012-001772
7. Inouye SK. Delirium in hospitalized older patients. Clin. Geriatr. Med. 1998;14:745–764.
8. Bruce, A. J., Ritchie, C. W., Blizard, R., Lai, R. & Raven, P. The incidence of delirium associated with orthopedic surgery: A meta-analytic review. Int. Psychogeriatr. 19, 197-214 (2007).
9. Girard, T. D. & Ely, E. W. Delirium in the critically ill patient. Handb. Clin. Neurol. 90, 39-56 (2008)
10. Inouye SK. Delirium in older persons. N. Engl. J. Med. 2006;354:1157–1165
11. Pisani, M. A., McNicoll, L. & Inouye, S. K. Cognitive impairment in the intensive care unit. N. Engl. J. Med. 24, 727-737 (2003)
12. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008 Jan 14;168(1):27-32. PubMed PMID: 18195192.
13. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
14. WHO Regional Offi ce for Europe. European hospital morbidity database. Copenhagen: World Health Organization, 2012.
15. Organisation for Economic Co-operation and Development. OECD health data 2012. Paris: Organisation for Economic Co-operation and Development, 2012.
16. Adamis D, Sharma N, Whelan PJ, Macdonald AJ. Delirium scales: a review of current evidence. Aging Ment Health 2010; 14: 543–55.
17. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA 2010; 304: 779–86.
18. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec 15;113(12):941-8. PubMed PMID: 2240918. Epub 1990/12/15.

19. Jin H. Han MD, MSc1,and Eduard E. Vasilevskis. Ultrabrief delirium assessments—are they ready for primetime? DOI: 10.1002/jhm.2478
20. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pract. 2003 Spring;17(1):31-50. PubMed PMID: 12751884. Epub 2003/05/20.
21. van Velthuijsen EL, et al. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. Int J Geriatr Psychiatry. 2016 Sep;31(9):974-89. doi: 10.1002/gps.4441. Epub 2016 Feb 21.
22. 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):249-54. PubMed PMID: 18707947. Epub 2008/08/19.
23. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord. 1999 Sep-Oct;10(5):393-400. PubMed PMID: 10473946. Epub 1999/09/04.
24. AGS/NIA Delirium Conference Writing Group PC, Faculty: The American Geriatrics Society/National Institute on Aging Bedside-to-Bench Conference: Research Agenda on Delirium in Older Adults. Journal of the American Geriatrics Society 2015, 63(5):843-852.
25. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM: Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society 2016, 64(4):705-714.
26. Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. Neurotherapeutics. 2012 Jan;9(1):158-75. doi: 10.1007/s13311-011-0102-9.
27. Young J, Leentjens AF, George J, Olofsson B, Gustafson Y. Systematic approaches to the prevention and management of patients with delirium. J Psychosom Res. 2008 Sep;65(3):267-72. PubMed PMID: 18707950.
28. Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. Psychosomatics. 2013 Mar-Apr;54(2):124-31. PubMed PMID: 23380670.
29. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005 Oct;53(10):1658-66. PubMed PMID: 16181163.
30. Kishi T, et al. J Neurol Neurosurg Psychiatry 2016;87:767–774. doi:10.1136/jnnp-2015-311049
31. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012;344:e420. PubMed PMID: 22323509. Pubmed Central PMCID: 3276486.
32. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med. 1993 Sep 15;119(6):474-81. PubMed PMID: 8357112.

33. Carrasco MP, Villarroel L, Andrade M, et al. Development and validation of a delirium predictive score in older people. Age Ageing. 2014;43(3):346-51.
34. Douglas VC, Hessler CS, Dhaliwal G, et al. The AWOL tool: derivation and validation of a delirium prediction rule. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2013;8(9):493-9.)
35. http://www.vmszorg.nl/ (Visited on 20/6/2017)
36. Guideline delirium adults and elderly (Richtlijn delier volwassen en ouderen 2013) http://www.vmszorg.nl/_library/24018/Richtlijn%20Delier%20Volwassenen%20en%20ouderen%202014.pdf
37. Collins N, Blanchard MR, Tookman A, Sampson EL: Detection of delirium in the acute hospital. Age Ageing 2010, 39(1):131-135.
38. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST, Jr., Leslie DL, Agostini JV: A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. Journal of the American Geriatrics Society 2005, 53(2):312-318.
39. van Gemert LA, Schuurmans MJ. The Neecham Confusion Scale and the Delirium Observation Screening Scale: Capacity to discriminate and ease of use in clinical practice. BMC Nursing 2007;6:3.
40. The Delirium Observation Screening scale recognizes delirium early after cardiac surgery Eur J Cardiovasc Nurs. 2009 Oct;8(4):309-14

Table 1. DElirium MOdel and cut-off point

DEMO-score = 1/(1+e-(Linear predictor)) DEMO score > 14.1% → Increased rrisk at delirium DEMO score ≤ 14.1% → No increased risk at delirium
Linear predictor = -8.823 + (0.081*V1) + (0.031*V2) + (0.248*V3) + (1.123*V4) + (0.286*V5) + (1.963*V6) + (0.359*V7) + (1.199*V8) + (0.413*V9) + (0.103*V10) V1 = Age (years) V2 = Polypharmacy (number of drugs) V3 = Anxiolytics (ATC N05B) V4 = Anti-dementia (ATC N06D) V5 = Antidepressives (ATC N06A) V6 = Antiparkinson's ATC (N04) V7 = Antidiabetic's (ATC A10) V8 = Psychopharmaca (ATC N05A) V9 = Analgetics (ATC N02A) V10 = Sleepmedication (ATC N05C)

* (ATC) Anatomical Therapeutic Chemical classification system (https://www.whocc.no/atc_ddd_index/)

Table 2. Test results of the prediction model (DEMO positive or negative) and diagnosis (delirium during admission or no-delirium during admission) within 1, 3 and 5 days after DEMO analysis.

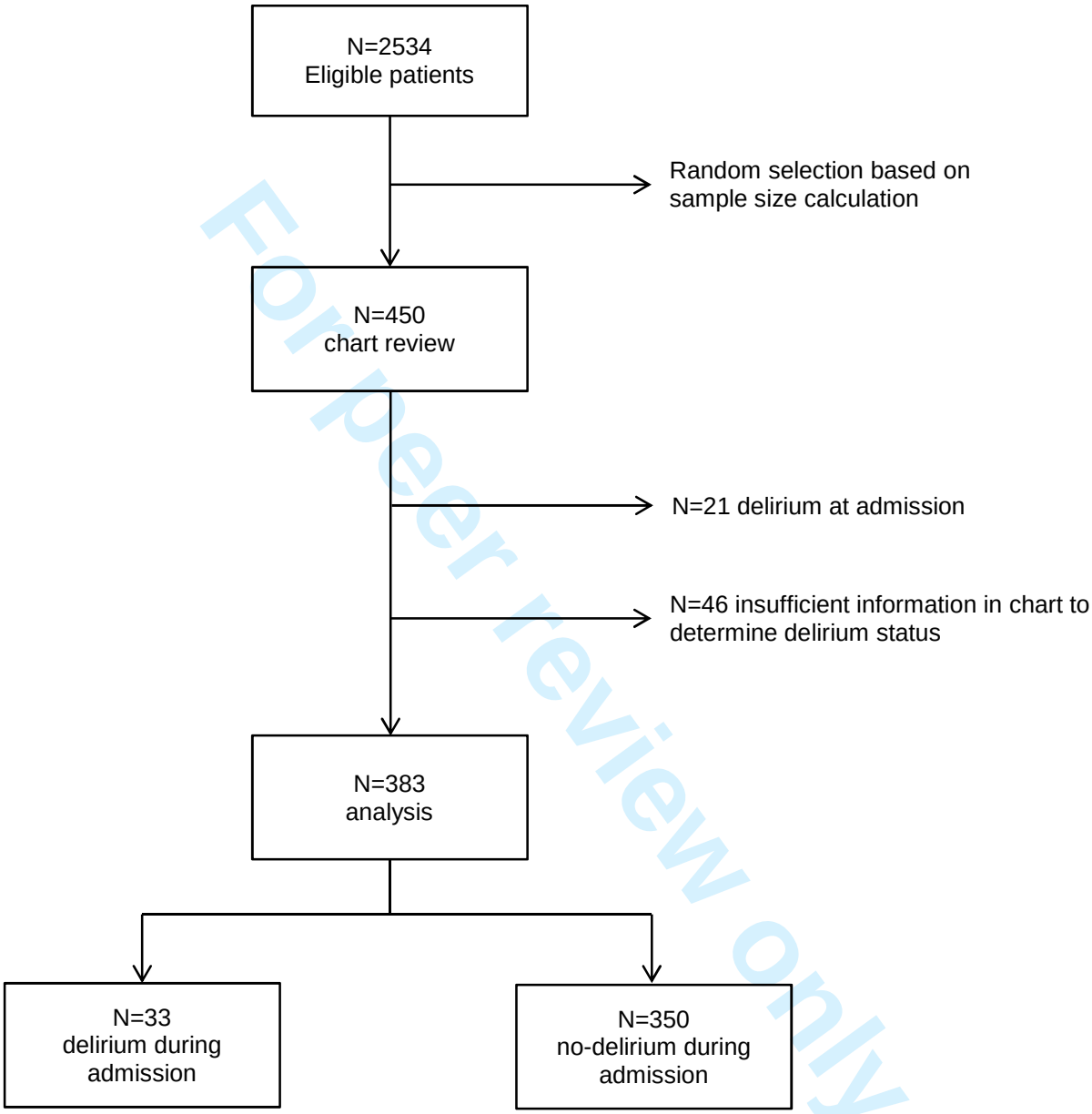
	Delirium within 1 day after DEMO	No-delirium within 1 day after DEMO	Delirium within 3 days after DEMO	No-delirium within 3 days after DEMO	Delirium within 5 days after DEMO	No-delirium within 5 days after DEMO
DEMO Positive	54	71	69	56	81	44
DEMO Negative	8	250	11	247	17	241

Table 3. Estimates of the prevalence, sensitivity, specificity, PPV, NPV, and likelihood ratios with corresponding 95% confidence intervals 1, 3 and 5 days after DEMO analysis.

	Day 1 after DEMO analysis			Day 3 after DEMO analysis			Day 5 after DEMO analysis		
	Estimated value	95% confidence interval		Estimated value	95% confidence interval		Estimated value	95% confidence interval	
		Lower limit	Upper limit		Lower limit	Upper limit		Lower limit	Upper limit
Prevalence	16.2%	0.127	0.204	18.8%	0.150	0.221	25.6%	0.213	0.303
Sensitivity	87.1%	0.756	0.939	84.2%	0.732	0.915	82.7%	0.734	0.893
Specificity	77.9%	0.729	0.822	81.5%	0.766	0.856	84.5%	0.797	0.884
PPV	43.20%*	0.345	0.524	51.3%*	0.419	0.607	64.8%*	0.557	0.730
NPV	96.90%	0.938	0.986	95.7%	0.922	0.977	93.4%	0.895	0.960
LR +	3.938	3.140	4.939	4.560	3.526	5.898	5.354	4.020	7.129
LR -	0.166	0.087	0.317	0.193	0.112	0.332	0.205	0.133	0.316

*PPV: Statistically different $p < 0.001$ for all three comparisons (1 vs 3 days, 1 vs 5 days, 3 vs 5 days)

Figure 1. Flow diagram inclusion



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5	
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	4-5	
Bias	9	Describe any efforts to address potential sources of bias	-	
Study size	10	Explain how the study size was arrived at	4	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	Table 2
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	5-6
		(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	Table 3
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	Table 2
		(*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	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
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	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-7
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
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	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.