

Key components of the delirium syndrome and mortality: greater impact of acute change and disorganised thinking in a prospective cohort study.

RA Diwell, D Davis, V Vickerstaff, EL Sampson

Authors

Rachel A Diwell, Division of Psychiatry, Faculty of Brain Sciences, UCL, Gower Street, London, WC1E 6BT
uctvrad@ucl.ac.uk

Dr Daniel Davis, Senior Clinical Researcher, MRC Unit for Lifelong Health and Ageing at UCL, 33 Bedford Place, London, WC1B 5JU
daniel.davis@ucl.ac.uk

Victoria Vickerstaff, Research Associate, Marie Curie Palliative Care Research Department, Division of Psychiatry, Faculty of Brain Sciences, UCL, Gower Street, London, WC1E 6BT and The Research Department of Primary Care and Population Health, UCL, Rowland Hill Street, London, NW3 2PF
v.vickerstaff@ucl.ac.uk

Dr Elizabeth L Sampson, Reader, Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, Gower Street, London, WC1E 6BT and Barnet Enfield and Haringey Mental Health Trust Liaison Psychiatry Team, North Middlesex University Hospital, London, N18 1QX
e.sampson@ucl.ac.uk

Corresponding author

Dr Elizabeth L Sampson, Reader, Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, Gower Street, London, WC1E 6BT,
e.sampson@ucl.ac.uk

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1 ABSTRACT

2 **Background:** Delirium increases the risk of mortality during an acute hospital admission. Full
3 syndromal delirium (FSD) is associated with greatest risk and subsyndromal delirium (SSD) is
4 associated with intermediate risk, compared to patients with no delirium – suggesting a dose-
5 response relationship. It is not clear how individual diagnostic symptoms of delirium influence the
6 association with mortality. Our objectives were to measure the prevalence of FSD and SSD, and
7 assess the effect that FSD, SSD and individual symptoms of delirium (from the Confusion Assessment
8 Method-short version (s-CAM)) have on mortality rates.

9 **Methods:** Exploratory analysis of a prospective cohort (aged ≥ 70 years) with acute (unplanned)
10 medical admission (4/6/2007-4/11/2007). The outcome was mortality (data censored 6/10/2011).
11 The principal exposures were FSD and SSD compared to no delirium (as measured by the CAM),
12 along with individual delirium symptoms on the CAM. Cox regression was used to estimate the
13 impact FSD and SSD and individual CAM items had on mortality.

14 **Results:** The cohort (n=610) mean age was 83 (SD 7); 59% were female. On admission, 11% had FSD
15 and 33% had SSD. Of the key diagnostic symptoms for delirium, 17% acute onset, 19% inattention,
16 17% disorganised thinking and 17% altered level of consciousness. Unadjusted analysis found FSD
17 had an increased hazard ratio (HR) of 2.31 (95%CI 1.71 , 3.12), for SSD the HR was 1.26 (1.00 , 1.59).
18 Adjusted analysis remained significant for FSD (1.55 95%CI 1.10 , 2.18) but nonsignificant for SSD
19 (HR=0.92 95% CI 0.70 , 1.19). Two CAM items were significantly associated with mortality following
20 adjustment: acute onset and disorganised thinking.

21 **Conclusion:** We observed a dose-response relationship between mortality and delirium, FSD had the
22 greatest risk and SSD having intermediate risk. The CAM items “acute-onset” and “disorganised
23 thinking” drove the associations observed. Clinically, this highlights the necessity of identifying
24 individual symptoms of delirium.

25

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26 BACKGROUND

27 Delirium is an acute neuropsychiatric syndrome affecting around 25% of general hospital patients
28 aged over 65 years [1-4]. It is characterised by acute onset and fluctuating course of disturbed
29 attention, consciousness, orientation, memory, arousal and, behaviour, and alterations in perception
30 and sleep cycle [5].

31
32 The aetiology of delirium is complex and multifactorial, including causes such as infection, sleep
33 deprivation, pain, specific organ failures and metabolic disturbances [1, 6-8]. Each individual's
34 threshold for delirium differs depending on predisposing risk factors such as age and frailty [9].

35
36 Many operational definitions exist for delirium, including formal classifications in the Diagnostic and
37 Statistical Manual of Mental Disorders (DSM) and algorithms such as the Confusion Assessment
38 Method (CAM) [10]. Intermediate states, subsyndromal delirium (SSD), can be defined where
39 individuals have symptoms of delirium but insufficient to meet the criteria for full syndromal
40 delirium (FSD) [11].

41
42 FSD is associated with a number of poor outcomes, such as longer hospital stays, increased risk of
43 post-hospital institutionalisation post-discharge, and accelerated cognitive decline [3, 8, 12-16]. FSD
44 carries its own risk of death, independent of an individual's exposure to established risk factors [3,
45 17-20]. The literature on SSD and adverse outcomes is less conclusive, partly because of variable
46 definitions of SSD in relation to symptom clusters and/or severity [11, 21, 22] .

47
48 It is possible that a dose-response relationship between FSD and mortality operates, such that SSD
49 carries intermediate risk [23]. However, this has often not been systematically evaluated in the same
50 cohort, using standardised definitions and maximally adjusting for a wide range of acute and chronic
51 health factors [21]. It is also not clear whether specific delirium symptoms drive the mortality

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relationship observed. In particular, no studies have estimated mortality rates associated with individual diagnostic items from rating scales such as the CAM.

54

Our objectives were to: (1) examine the prevalence of FSD and SSD in a representative cohort of older acute hospital in participants over the age of 70 years; (2) estimate the impact of FSD and SSD (as measured by the short CAM (s-CAM) on admission) on mortality rates and (3) assess the impact individual key diagnostic items on the s-CAM have on this relationship.

59

METHODS

Design

We undertook an exploratory retrospective analysis of data collected on a cohort of older people with acute medical illness admitted into hospital between 4/6/2007 to 4/11/2007. Characteristics of the cohort have been described previously [24]. In brief, participants were eligible for inclusion if they were: ≥ 70 years old with an unplanned medical admission who were admitted >48 hours. All clinical assessments were conducted by psychiatrists within 72 hours of admission. Participants who lacked English language skills necessary to complete basic cognitive assessments were excluded. We sought verbal consent from participants or, if they lacked capacity to consent, verbal assent from their carers. The study involved the collection of routine clinical data that has subsequently been fully anonymised. The findings of these assessments were documented on the medical notes so that clinical teams could act on them if they wished. The exclusion of patients unable to give written informed consent or those without a relative to give assent for their participation may have caused selection bias, excluding the patient population we wished to study. The study and its verbal consent procedure was approved by the Royal Free Hospital NHS Trust Ethics Committee (06/Q0501/31).

Outcome

Mortality was flagged by the UK Office for National Statistics (ONS) (mortality data censored 6/10/2011).

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78 **Main exposures**

79 **Delirium**

80 Participants were assessed using the Confusion Assessment Method, short version (s-CAM), which
 81 details the following delirium features: (1) acute onset, (2) inattention, (3) disorganised thinking, (4)
 82 altered level of consciousness [25]. The s-CAM has high sensitivity of >94% and specificity >90% for
 83 the detection of delirium and accurately distinguishes between delirium and dementia [26]. FSD was
 84 defined as persons demonstrating abnormalities in features 1 + 2 + (3 or 4). SSD was defined as
 85 having one or more s-CAM symptoms, but not fulfilling criteria for FSD. All participants without
 86 symptoms of FSD or SSD were defined as 'no delirium'.

87

88 **Covariates**

89 Demographic data (age, sex, place of residence, ethnic origin and marital status) was collected from
 90 hospital records. Other assessments included the Charlson Co-morbidity Index [27, 28], Waterlow
 91 Scale [29] and a modified version of the Acute Physiology and Chronic Health Evaluation (APACHE II)
 92 [30-32](omitting the arterial blood gas). Severity of functional impairment prior to hospital
 93 admission was gathered from next of kin or other carers using the Functional Assessment Staging
 94 Scale (FAST) [33].

95

96 **Data analysis**

97 Differences in categorical and continuous variables according to delirium status were assessed using
 98 chi-square, ANOVA and Kruskal Wallis tests as appropriate. Continuous variables with skewed data
 99 (CCI and APACHE II scores) were categorised into standard quartiles for the final analysis.

100

101 Survival estimates for FSD, SSD and no delirium were compared using Kaplan-Meier curves and log-
 102 rank tests. Cox regression was used to examine the relationship between FSD, SSD and no delirium
 103 with mortality risk, sequentially adjusting for relevant confounders in a multivariable model. Finally,

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the relationship between each CAM criterion and mortality was estimated in the whole cohort, irrespective of syndromal status. Proportional hazard assumptions were met for all Cox regression analyses, confirmed by Schoenfeld Residuals ≥ 0.05 . Candidate prediction models were compared using Harrell's c statistics. Data were analysed using STATA version 12.

RESULTS

Study population

A total of 785 participants were recruited, of these, 75 participants had missing data and were excluded, leaving 710 participants assessed using the s-CAM at the time of admission. Exclusions occurred due to: incomplete/missing data (n=32, (5%)), being too ill (n=18, (2%)), untraceable (n=2, (1%)), unable to speak English sufficiently (n=25, (3%)), refusal to participate (n=23, (3%)). Therefore, 610 (86%) participants from the original sample were included (Figure 1).

[Figure 1 approximately here]

Mean age was 83 (sd 7) and over half were female (59%). A majority of the participants lived in their home (71%) and were of White British origin (70%) (Table 1).

A total of 69 (11%) participants had FSD, 202 (33%) had SSD and 339 (56%) had no delirium. The diagnostic symptom *inattention* had slightly higher prevalence (19%) compared to *acute onset*, *disorganised thinking* and *altered level of consciousness* (17%). Median CCI score was 2 (IQR 3) and APACHE II score was 11 (IQR 4), and the mean Waterlow score was 13 (6) (Table 1).

[Table 1 approximately here]

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Prevalence of FSD and SSD increased with age, though there was no association with gender. FSD and SSD became more prevalent as age increased. Participants with FSD and SSD were more likely to live in nursing or sheltered accommodation. There was an overall higher prevalence of having a pre-existing dementia diagnosis, higher Waterlow scores, higher APACHE II scores and greater length of hospital stay.

Kaplan-Meier curves showed delirium was associated with reduced survival and that participants with FSD had greatest reduction in survival estimates compared to participants with no symptoms, and SSD had intermediate reduction (<0.001) (Figure 2). FSD had a median survival time of 5 months, compared to 21 months for SSD and 31 months for participants with no symptoms (Table 2).

[Figure 2 approximately here]

[Table 2 approximately here]

In unadjusted Cox models, participants with FSD had a higher mortality risk (HR 2.31 95%CI 1.71 , 3.12) compared with participants with no delirium. Participants with SSD had 1.26 (95% CI 1.00 , 1.59) greater risk of mortality compared to participants with no symptoms. Each adjustment variable (age, gender, CCI, Waterlow and APACHE II) was independently related to death ($p<0.001$), except gender ($p=0.684$) (Table 4). Sequential adjustment showed that the associations between FSD and mortality remained after adjusting for age, sex, CCI, Waterlow and APACHE II (HR 1.55 95%CI 1.10 , 2.18). The same sequence of adjustments for SSD and mortality showed greater attenuation (HR = 0.92 95% CI 0.70 , 1.19). Unadjusted Cox models showed each s-CAM item was associated with higher mortality ($p<0.001$).

After sequential adjustment for age, sex, CCI, Waterlow and APACHE II, *acute onset* (HR 1.41 95% CI 1.07 , 1.86) and *disorganised thinking* (HR 1.42 95% CI 1.05 , 1.92) were associated with mortality,

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whereas this was no longer the case for estimates for *inattention* (HR 1.24 95% CI 0.92 , 1.67) and *altered level of consciousness* (HR 1.33 95% CI 0.98 , 1.79). C-statistics for all models were very close (0.66 to 0.67), suggesting comparable predictive ability for this set of variables.

[Table 3 approximately here]

DISCUSSION

We demonstrated a dose-response relationship between SSD, FSD and mortality, even after adjustment for a wide range of acute and chronic health factors. Individual s-CAM items contribute differentially to this relationship; *acute onset* and *disorganised thinking* appear to drive the association. Taken together, these findings emphasise that neuropsychiatric symptoms that arise in the context of acute illness in older people identified individuals at higher risk for dying.

This study had several strengths. The large cohort size and prospective data in a diverse socio-economic and ethnic population benefited from standardised assessments by experts and automatic notification of deaths from the UK Office of National Statistics. Data was collected within a 72 hour time-period after admission so it is not possible to establish whether cases of delirium were prevalent or incident and although the s-CAM has been shown to have good interrater reliability of 0.81-1.00 [34] we do not have data on this for our study. In keeping with other studies, limitations include the possibility of residual confounding. We identified FSD and SSD at a prevalence and associated with adverse outcomes consistent with the range established from systematic reviews [1, 2].

Participants with SSD had outcomes intermediate to those with no delirium and FSD – particularly in relation to acute illness severity, poor prognosis and outcomes, suggesting a dose-response relationship between delirium severity and mortality risk, which is in keeping with previous work [21,

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23]. However, few other studies have been able to establish these associations while also accounting for a wide range of acute and chronic health factors.[35]

There is little literature exploring the individual mortality risk associated with each key symptom of delirium. We found each individual item on the short s-CAM was significantly associated with mortality, though *acute onset* and *disorganised thinking* had greater risk of mortality when all items were mutually adjusted.

A number of underlying mechanisms may explain the observed dose-response relationship between delirium and mortality. The causes of delirium can persist, which itself could lead to protracted delirium, prolonged hospital stays [17], and increased risk of death [36]. In turn, longer hospital stays could expose patients to a greater risk of iatrogenic harm [37, 38] for example: participants with hypoactive delirium have a greater risk of aspiration pneumonia, whereas participants with hyperactive delirium have greater risk of falls [39, 40] which in turn could cause longer hospital stays, further health deterioration and greater risk of death. Disorganised thinking could be a particularly adverse symptom because it may represent more profound neurocognitive disturbance particularly detrimental in frail, older participants predisposed to chronic and severe physical illness [3, 35, 41, 42].

Conclusions

Emergency admission of an older patient presenting with FSD or SSD is a strong potential indicator of risk of death. Clinically it is important to be aware that each key symptom of FSD is strongly related to death, and participants presenting with just one symptom still carry an increased risk – highlighting the necessity of recognising each symptom separately. Better awareness of the mortality risk associated with delirium would strengthen arguments for early intervention, better

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207 treatment and quality of care, considering care plans and encouragement of discussion of prognosis
208 with the patient and/or carer.

209

210

211 LIST OF ABBREVIATIONS

- 212 • ANOVA- analysis of variance
- 213 • APACHE-11 – Acute Physiology and Chronic Health Evaluation
- 214 • CAM – Confusion Assessment Method
- 215 • S-CAM- Short Confusion Assessment Method
- 216 • CCI – Charlson Comorbidity Index
- 217 • DSM-Diagnostic and Statistical Manual of Mental Disorders
- 218 • FAST-Functional Assessment staging
- 219 • FSD – full syndromal delirium
- 220 • HR-hazard ratio
- 221 • IQR-interquartile range
- 222 • sd –standard deviation
- 223 • ONS- Office for National Statistics
- 224 • SSD – subsyndromal delirium

225

226 DECLARATIONS

227 Ethnical approval and consent to participation

228 The study was approved by the Royal Free Hospital NHS Ethics Committee (06/Q0501/31).

229

230 Consent for publication

231 Not applicable.

232

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233 **Availability of data and materials**

234 The datasets used and/or analysed during the current study available from the corresponding author
235 on reasonable request.

236 **Competing interests**

237 The authors declare that they have no competing interests.

238

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245 study, data collection, analysis, and interpretation of the data and in writing the manuscript.

246

247 **Authors' Contributions**

248 ELS conducted the original study. RAD, VV and DD planned the data analysis. RAD analysed and
249 interpreted data. ELS, DD and VV assisted with interpretation of the data outcomes. All authors
250 contributed to the writing of the manuscript and approved the final manuscript.

251

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260 REFERENCES

261

- 262 1. Siddiqi N, House AO, Holmes JD: **Occurrence and outcome of delirium in medical in-**
263 **patients: a systematic literature review.** *Age Ageing* 2006, **35**(4):350-364.
- 264 2. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y: **Incidence, risk factors and consequences of**
265 **ICU delirium.** *Intensive Care Med* 2007, **33**(1):66-73.
- 266 3. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA: **Delirium in**
267 **elderly patients and the risk of postdischarge mortality, institutionalization, and dementia:**
268 **a meta-analysis.** *JAMA* 2010, **304**(4):443-451.
- 269 4. Collins N, Blanchard MR, Tookman A, Sampson EL: **Detection of delirium in the acute**
270 **hospital.** *Age Ageing* 2010, **39**(1):131-135.
- 271 5. American Psychiatric Association: **Diagnostic and Statistical Manual of Mental Disorders,**
272 **4th Edition edn.** Washington DC: American Psychiatric Association; 1994.
- 273 6. Leslie DL, Zhang Y, Holford TR, Bogardus ST, Leo-Summers LS, Inouye SK: **Premature death**
274 **associated with delirium at 1-year follow-up.** *ArchInternMed* 2005, **165**(14):1657-1662.
- 275 7. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK: **The interface between delirium**
276 **and dementia in elderly adults.** *Lancet Neurol* 2015, **14**(8):823-832.
- 277 8. Ward G, Perera G, Stewart R: **Predictors of mortality for people aged over 65 years**
278 **receiving mental health care for delirium in a South London Mental Health Trust, UK: a**
279 **retrospective survival analysis.** *Int J Geriatr Psychiatry* 2015, **30**(6):639-646.
- 280 9. MacLullich AM, Anand A, Davis DH, Jackson T, Barugh AJ, Hall RJ, Ferguson KJ, Meagher DJ,
281 Cunningham C: **New horizons in the pathogenesis, assessment and management of**
282 **delirium.** *Age Ageing* 2013, **42**(6):667-674.
- 283 10. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI: **Clarifying confusion: the**
284 **confusion assessment method. A new method for detection of delirium.** *AnnInternMed*
285 1990, **113**(12):941-948.
- 286 11. Sepulveda E, Franco JG, Trzepacz PT, Gaviria AM, Meagher DJ, Palma J, Vinuelas E, Grau I,
287 Vilella E, de Pablo J: **Delirium diagnosis defined by cluster analysis of symptoms versus**
288 **diagnosis by DSM and ICD criteria: diagnostic accuracy study.** *BMC Psychiatry* 2016, **16**:167.
- 289 12. Dasgupta M, Dumbrell AC: **Preoperative risk assessment for delirium after noncardiac**
290 **surgery: a systematic review.** *J Am Geriatr Soc* 2006, **54**(10):1578-1589.
- 291 13. Morandi A, Jackson JC, Ely EW: **Delirium in the intensive care unit.** *Int Rev Psychiatry* 2009,
292 **21**(1):43-58.
- 293 14. Cole MG: **Persistent delirium in older hospital patients.** *Curr Opin Psychiatry* 2010,
294 **23**(3):250-254.
- 295 15. Davis DH, Muniz-Terrera G, Keage HA, Stephan BC, Fleming J, Ince PG, Matthews FE,
296 Cunningham C, Ely EW, MacLullich AM *et al*: **Association of Delirium With Cognitive Decline**
297 **in Late Life: A Neuropathologic Study of 3 Population-Based Cohort Studies.** *JAMA*
298 *Psychiatry* 2017, **74**(3):244-251.
- 299 16. Davis DH, Muniz-Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE, Cunningham C,
300 Polvikoski T, Sulkava R, MacLullich AM *et al*: **Delirium is a strong risk factor for dementia in**
301 **the oldest-old: a population-based cohort study.** *Brain* 2012, **135**(Pt 9):2809-2816.
- 302 17. Kiely DK, Marcantonio ER, Inouye SK, Shaffer ML, Bergmann MA, Yang FM, Fearing MA,
303 Jones RN: **Persistent delirium predicts greater mortality.** *J Am Geriatr Soc* 2009, **57**(1):55-
304 61.

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18. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P: **Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study.** *JGenInternMed* 1998, **13**(4):234-242.
19. Salluh JJ, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, Serafim RB, Stevens RD: **Outcome of delirium in critically ill patients: systematic review and meta-analysis.** *BMJ* 2015, **350**:h2538.
20. Lindsay J, Rockwood K, Rolfson D: **The epidemiology of delirium.** In: *Delirium in Old Age.* edn. Edited by Lindsay J, Rockwood K, Macdonald A. Oxford: Oxford University Press; 2002: 27-50.
21. Cole MG, Ciampi A, Belzile E, Dubuc-Sarrasin M: **Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes.** *Int J Geriatr Psychiatry* 2013, **28**(8):771-780.
22. Ouimet S, Riker R, Bergeron N, Cossette M, Kavanagh B, Skrobik Y: **Subsyndromal delirium in the ICU: evidence for a disease spectrum.** *Intensive Care Med* 2007, **33**(6):1007-1013.
23. Marcantonio ER, Kiely DK, Simon SE, John Orav E, Jones RN, Murphy KM, Bergmann MA: **Outcomes of older people admitted to postacute facilities with delirium.** *J Am Geriatr Soc* 2005, **53**(6):963-969.
24. Sampson EL, Blanchard MR, Jones L, Tookman A, King M: **Dementia in the acute hospital: prospective cohort study of prevalence and mortality.** *BrJPsychiatry* 2009, **195**(1):61-66.
25. Inouye SK: **The Short Confusion Assessment Method (Short CAM): Training Manual and Coding Guide.** . In. Boston: Hospital Elder Life Program; 2014.
26. van Velthuisen EL, Zwakhalen SM, Warnier RM, Mulder WJ, Verhey FR, Kempen GI: **Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review.** *Int J Geriatr Psychiatry* 2016, **31**(9):974-989.
27. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40**(5):373-383.
28. Charlson M, Szatrowski TP, Peterson J, Gold J: **Validation of a combined comorbidity index.** *J Clin Epidemiol* 1994, **47**(11):1245-1251.
29. Waterlow J: **Pressure sores: a risk assessment card.** *Nursing Times* 1985, **81**(48):49-55.
30. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system.** *Crit Care Med* 1985, **13**(10):818-829.
31. Adamis D, Treloar A, Darwiche FZ, Gregson N, Macdonald AJ, Martin FC: **Associations of delirium with in-hospital and in 6-months mortality in elderly medical inpatients.** *Age Ageing* 2007, **36**(6):644-649.
32. Man SY, Chan KM, Wong FY, Wong KY, Yim CL, Mak PS, Kam CW, Lau CC, Lau FL, Graham CA *et al*: **Evaluation of the performance of a modified Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system for critically ill patients in emergency departments in Hong Kong.** *Resuscitation* 2007, **74**(2):259-265.
33. Reisberg B, Sclan SG, Franssen E, Kluger A, Ferris S: **Dementia staging in chronic care populations.** *Alzheimer Dis Assoc Disord* 1994, **8 Suppl 1**:S188-205.
34. Wei LA, Fearing MA, Sternberg EJ, Inouye SK: **The Confusion Assessment Method: a systematic review of current usage.** *J Am Geriatr Soc* 2008, **56**(5):823-830.
35. Dani M, Owen LH, Jackson TA, Rockwood K, Sampson EL, Davis D: **Delirium, frailty and mortality: interactions in a prospective study of hospitalized older people.** *J Gerontol A Biol Sci Med Sci* 2017.
36. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, Group SS: **Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients.** *Crit Care Med* 2010, **38**(12):2311-2318.

Delirium subtypes and mortality

37. O'Keeffe S, Lavan J: **The prognostic significance of delirium in older hospital patients.** *J Am Geriatr Soc* 1997, **45**(2):174-178.
38. Permpongkosol S: **Iatrogenic disease in the elderly: risk factors, consequences, and prevention.** *Clin Interv Aging* 2011, **6**:77-82.
39. Lakatos BE, Capasso V, Mitchell MT, Kilroy SM, Lussier-Cushing M, Sumner L, Reppe-Delisi J, Kelleher EP, Delisle LA, Cruz C *et al*: **Falls in the general hospital: association with delirium, advanced age, and specific surgical procedures.** *Psychosomatics* 2009, **50**(3):218-226.
40. Marcantonio E, Ta T, Duthie E, Resnick NM: **Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair.** *Journal of the American Geriatrics Society* 2002, **50**(5):850-7, 2002 May(32 ref) 2002(5):850-857.
41. MacLullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C: **Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses.** *J Psychosom Res* 2008, **65**(3):229-238.
42. van Gool WA, van de Beek D, Eikelenboom P: **Systemic infection and delirium: when cytokines and acetylcholine collide.** *Lancet* 2010, **375**(9716):773-775.

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Table 1: Cohort characteristics by CAM delirium diagnosis

Variables <i>n</i> (%), <i>m</i> (sd), median (IQR)	Total	CAM delirium status			<i>p</i> value*
<i>n</i> , (%)	610(100)	FSD 69(11)	SSD 202(33)	No delirium 339(56)	
Demographics					
Gender, (%)					
Male	251(41)	24(10)	70(28)	157(62)	0.015*
Female	359(59)	45(12)	132(37)	182(51)	
Age in years, (%)					
70-79	227(37)	13(6)	63(28)	151(66)	<0.001*
80-89	265(44)	35(13)	85(32)	145(55)	
90+	118(19)	21(18)	54(46)	43(36)	
Type of residence, (%)					
House	434(71)	31(7)	122(28)	281(65)	<0.001*
Residential	46(8)	4(9)	12(26)	30(65)	
Nursing home	42(7)	12(29)	20(48)	10(24)	
Sheltered	88(14)	22(25)	48(55)	18(20)	
Ethnicity, (%)					
White	428(70)	11(12)	144(34)	234(55)	0.816
Marital status, (%)					
Married	198(33)	15(8)	58(29)	125(63)	0.096
Single	87(14)	8(9)	30(35)	49(56)	
Widowed	282(46)	40(14)	101(36)	141(50)	
Divorced	36(6)	4(11)	10(28)	22(61)	
Unknown	7(1)	2(28)	3(43)	2(29)	

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Smoking status, (%)					
Never	281(46)	40(14)	105(37)	136(48)	<0.001*
Ex	269(44)	22(8)	83(31)	164(61)	
Current	55(9)	4(7)	13(24)	38(69)	
Unknown	5(1)	3(60)	1(20)	1(20)	
Clinical Characteristics					
Presence of CAM individual item acute onset, (%)**	99(17)	69(100)	30(15)	0(0)	<0.001*
Presence of CAM individual item inattention, (%)**	108(19)	69(100)	39(19)	0(0)	<0.001*
Presence of CAM individual item disorganized thinking, (%)**	97(17)	65(94)	32(16)	0(0)	<0.001*
Presence of CAM individual item, altered level of consciousness, (%)**	99(17)	63(91)	36(19)	0(0)	<0.001*
Psychiatric history admissions, (%)**					
None known	483(80)	47(10)	149(31)	287(59)	0.047*
Anxiety	6(1)	0(0)	3(50)	3(50)	
Depression and anxiety	12(2)	2(17)	5(42)	5(42)	
Depression	86(14)	17(20)	37(43)	32(37)	
Alcohol	9(1)	1(11)	4(44)	4(44)	
Bipolar	3(1)	0(0)	1(33)	2(67)	
Psychosis	8(1)	2(25)	3(37)	3(38)	
Dementia status, (%)					
Yes	159(26)	45(28)	84(53)	30(19)	<0.001*
No	451(74)	24(5)	118(26)	309(69)	

Delirium subtypes and mortality

Functional Assessment Staging Score, (%)					
1. No functional impairment	263(43)	3(1)	35(13)	225(86)	<0.001*
2-5. Subjective functional deficit, objective functional deficit, difficulties with activities of daily living	179(29)	13(7)	74(41)	92(51)	
6a-c. Help required getting dressed, toileting or personal hygiene	66(11)	24(36)	29(44)	13(20)	
6d-e. Double incontinence	62(10)	20(32)	36(58)	6(10)	
7a-f. Speaks limited vocabulary, can no longer walk, sit up, hold up head	40(7)	9(23)	28(70)	3(7)	
Waterlow score, mean (sd)** N=605	13(6)	17(7)	15(7)	11(5)	<0.001*
Incontinence, (%)**					
None	460(75)	32(7)	120(26)	308(67)	<0.001*
Urine	58(10)	14(24)	28(48)	16(28)	
ICD on admission	16(3)	4(25)	6(38)	6(37)	
Double	75(12)	19(25)	48(64)	8(11)	
Pressure sores, (%)					
Yes	58(10)	14(24)	36(62)	8(14)	<0.001*
No	551(90)	55(10)	166(30)	330(60)	
Unknown	1(0)	0(0)	0(0)	1(100)	
Charlson Comorbidity Index score, median (IQR)	2(3)	3(2)	3(2)	2(3)	0.067*
APACHE II score, median (IQR)**N=593	11(4)	14(5)	12(4)	11(4)	<0.001*
Commonest diagnosis on admission, (%)					
ACS	56(9)	3(5)	10(18)	43(77)	<0.001*
COPD	37(6)	2(5)	9(24)	26(70)	
UTI	54(9)	11(20)	24(44)	19(35)	
Pneumonia	91(15)	20(22)	42(46)	29(32)	
Other	372(61)	33(9)	117(31)	222(60)	

Delirium subtypes and mortality

Length of admission, median (IQR)** N=609	8(13)	14(20)	9(13)	7(10)	<0.001*
Survival time – days, median (IQR)** N=357	157(457)	125(355)	143(454)	194(495)	0.022*

Table 1 end.

Cohort characteristics stratified by delirium status: full syndromal delirium, subsyndromal delirium and no delirium. Count and percentage was calculated for categorical variables, mean and standard deviation was calculated for continuous variables normally distributed, and median and interquartile range was calculated for continuous variables with skewed distribution. Pearson Chi square, Analysis of Variance and Kruskal Wallis were used where appropriate. Significance level was set at <0.05.

sd, standard deviation; n, number of participants; IQR, interquartile range; *, significant; **, complete case analysis; ACS, Acute Cardiac Syndrome; COPD, chronic obstructive pulmonary disease; UTI, urinary tract infection; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Delirium subtypes and mortality

Table 2: Mortality by delirium status (95%CI)			
	Delirium status		
	<i>Full delirium n= 56</i>	<i>Subsyndromal delirium n=122</i>	<i>No delirium n=179</i>
<i>Survival time%</i>			
<6 months	62.50 (0.49 , 0.76)	54.92 (0.46 , 0.64)	49.72 (0.42 , 0.57)
>6 months	37.50 (0.24 , 0.51)	45.08 (0.36 , 0.54)	50.28 (0.43 , 0.58)
<i>Median survival time (months)</i>	5.03 (2.30 , 13.93)	21.16 (13.11 , 29.04)	31.21 (23.66 , NA)

Percentage of eligible patients and 95% confidence intervals stratified into survival time less than or more than 6 months following hospital admission. Death was flagged by the UK Office of National Statistics and certified by a death certificate. Median length and 95% confidence intervals for survival time was calculated following hospital admission. Complete case = 357.

<, less than; >, more than; NA, not available.

Delirium subtypes and mortality

Table 3: Adjusted cox regression model for the effect of the 4 core symptoms of delirium status on mortality, sequentially adjusted for clinically relevant covariates

HR (95%CI) <i>p</i> -value.						
	<i>None (unadjusted)</i>	+Age	+ Gender	+ CCI	+ Waterlow	+ APACHE II
Delirium key core symptoms						
Acute onset (<i>n</i> =583)	1.88 (1.45 , 2.42) <i>p</i> <0.001*	1.80 (1.39 , 2.33) <i>p</i> <0.001*	1.80 (1.39 , 2.33) <i>p</i> <0.001*	1.76 (1.35 , 2.29) <i>p</i> <0.001*	1.46 (1.11 , 1.91) <i>p</i> =0.007*	1.41 (1.07 , 1.86) <i>p</i> =0.016*
Inattention (<i>n</i> =576)	1.80 (1.40 , 2.32) <i>p</i> <0.001*	1.74 (1.35 , 2.25) <i>p</i> <0.001*	1.75 (1.36 , 2.26) <i>p</i> <0.001*	1.73 (1.34 , 2.24) <i>p</i> <0.001*	1.33 (1.01 , 1.77) <i>p</i> =0.044*	1.24 (0.92 , 1.67) <i>p</i> =0.152
Disorganised thinking (<i>n</i> =563)	2.06 (1.59 , 2.67) <i>p</i> <0.001*	1.97 (1.51 , 2.55) <i>p</i> <0.001*	2.01 (1.54 , 2.54) <i>p</i> <0.001*	1.94 (1.48 , 2.54) <i>p</i> <0.001*	1.52 (1.14 , 2.04) <i>p</i> =0.005*	1.42 (1.05 , 1.92) <i>p</i> =0.024*
Altered level of consciousness (<i>n</i> =588)	2.04 (1.58 , 2.63) <i>p</i> <0.001*	1.95 (1.50 , 2.52) <i>p</i> <0.001*	1.96 (1.51 , 2.53) <i>p</i> <0.001*	1.82 (1.40 , 2.37) <i>p</i> <0.001*	1.41 (1.06 , 1.88) <i>p</i> =0.018*	1.33 (0.98 , 1.79) <i>p</i> =0.063

Cox proportional hazard regression analysis for survival estimates for the four key core symptoms of full syndromal delirium. Unadjusted model complete case = 610. The same sample was used for the sequentially adjusted Cox proportional hazards regression model (age, gender, CCI, Waterlow and APACHE II). APACHE II and CCI scores were split into quartiles for the purpose of the analysis. There was no evidence of interactions, these, therefore were no longer considered. Proportional hazard assumptions were met, confirmed by Schoenfeld residuals ≥ 0.05 . Significance level set at <0.05.

*CAM, Confusion Assessment Method; HR, hazard ratios; CI, confidence intervals; *p*, significance level; N, number of participants; *, significant; CCI, Charlson Comorbidity Index; APACHE II, Acute Physiology and Chronic Health Evaluation II.*

Delirium subtypes and mortality

FIGURE TITLE AND LEGENDS

Figure 1 Title: Study flowchart.

Figure 1 Legend: Study flowchart showing the exclusion process and exclusion criteria for the study sample. 86% of the original sample were considered eligible for the study.

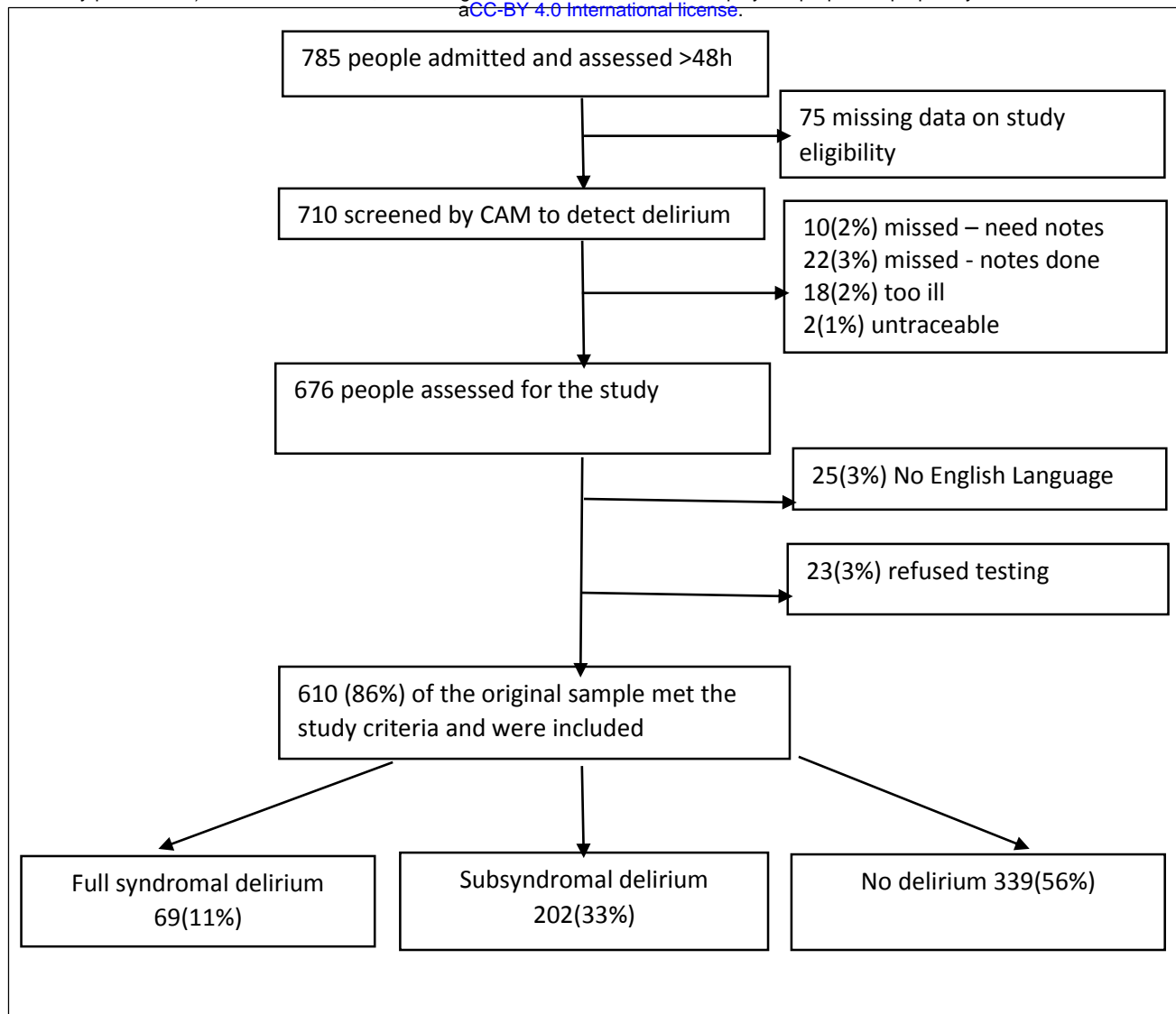
Figure 2 Title: Kaplan-Meier: Unadjusted survival estimates by delirium status

Figure 2 Legend: Kaplan Meier curves illustrate unadjusted survival estimates by delirium status. Full syndromal delirium is shown to have significant reduction in survival estimates, compared to patients no symptoms. It also shows that subsyndromal delirium has intermediate reduction in survival estimates compared against full syndromal delirium and no symptoms.

Delirium subtypes and mortality

Figure 1: Study flowchart

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Delirium subtypes and mortality

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Figure 2: Kaplan Meier curves unadjusted survival estimates by delirium status

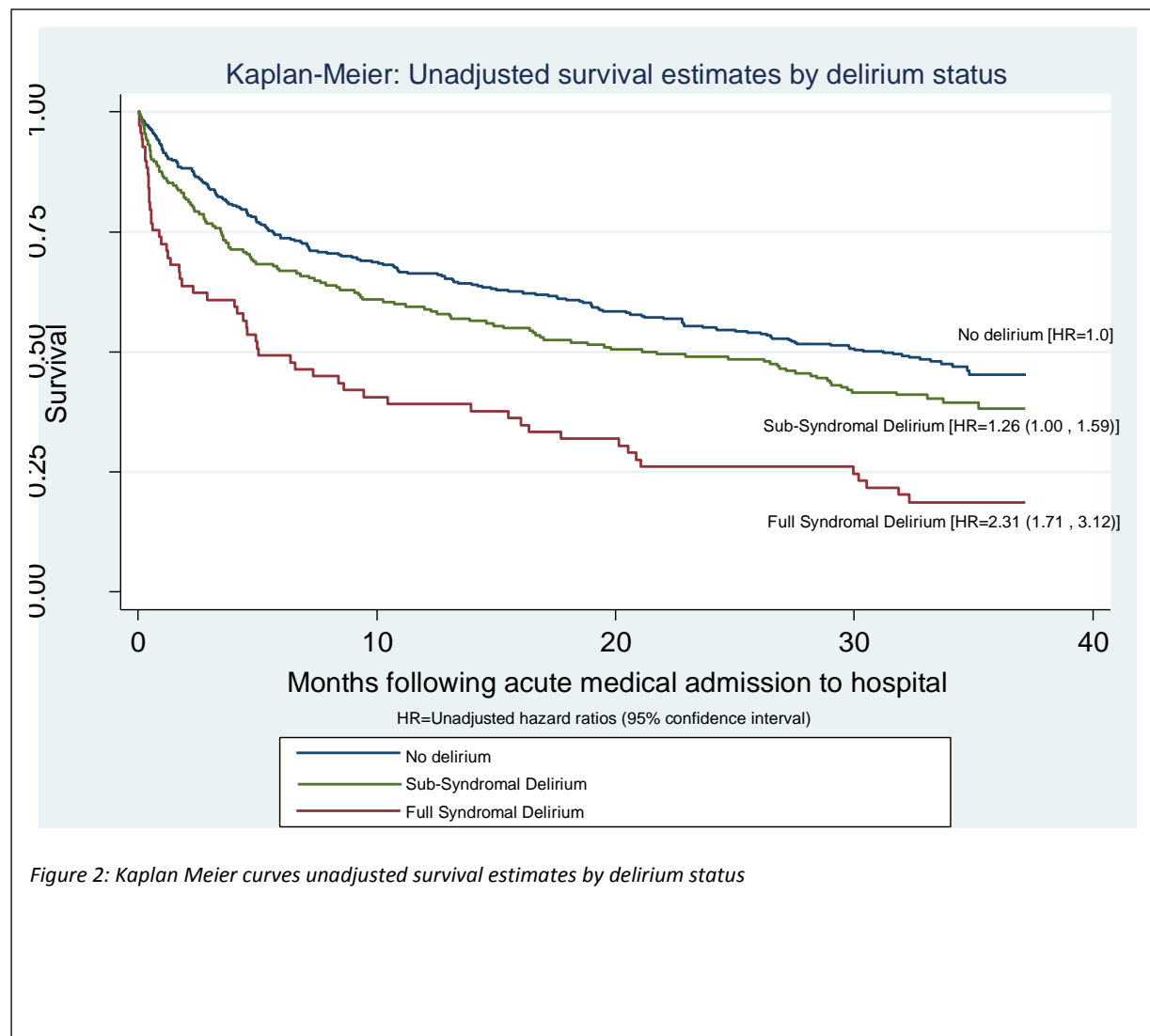


Figure 2: Kaplan Meier curves unadjusted survival estimates by delirium status