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

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ABSTRACT

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

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

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

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

BACKGROUND

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

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

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

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

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

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

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.

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).

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,

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]

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,

156 whereas this was no longer the case for estimates for *inattention* (HR 1.24 95% CI 0.92 , 1.67) and
157 *altered level of consciousness* (HR 1.33 95% CI 0.98 , 1.79). C-statistics for all models were very close
158 (0.66 to 0.67), suggesting comparable predictive ability for this set of variables.
159
160 *[Table 3 approximately here]*
161
162 **DISCUSSION**
163 We demonstrated a dose-response relationship between SSD, FSD and mortality, even after
164 adjustment for a wide range of acute and chronic health factors. Individual s-CAM items contribute
165 differentially to this relationship; *acute onset* and *disorganised thinking* appear to drive the
166 association. Taken together, these findings emphasise that neuropsychiatric symptoms that arise in
167 the context of acute illness in older people identified individuals at higher risk for dying.
168
169 This study had several strengths. The large cohort size and prospective data in a diverse socio-
170 economic and ethnic population benefited from standardised assessments by experts and automatic
171 notification of deaths from the UK Office of National Statistics. Data was collected within a 72 hour
172 time-period after admission so it is not possible to establish whether cases of delirium were
173 prevalent or incident and although the s-CAM has been shown to have good interrater reliability of
174 0.81-1.00 [34] we do not have data on this for our study. In keeping with other studies, limitations
175 include the possibility of residual confounding. We identified FSD and SSD at a prevalence and
176 associated with adverse outcomes consistent with the range established from systematic reviews [1,
177 2].
178
179 Participants with SSD had outcomes intermediate to those with no delirium and FSD – particularly in
180 relation to acute illness severity, poor prognosis and outcomes, suggesting a dose-response
181 relationship between delirium severity and mortality risk, which is in keeping with previous work [21,

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

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

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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Table 1: **Cohort characteristics by CAM delirium diagnosis**

Variables *n* (%), *m* (sd), median (IQR)	***Total***		***CAM delirium status***		***p* value***
		FSD	**SSD**	**No delirium**	
n, (%)	610(100)	69(11)	202(33)	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)	

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)	

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)	

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.*

Table 2: Mortality by delirium status (95%CI)			
	Delirium status		
	Full delirium n= 56	*Subsyndromal delirium n=122*	*No delirium n=179*
Survival time%			
<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)
Median survival time (months)	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.

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) *p*-value.						
Delirium key core symptoms	***None (unadjusted)***	**+Age**	**+ Gender**	**+ CCI**	**+ Waterlow**	**+ APACHE II**
Acute onset *(n=583)*	1.88 (1.45 , 2.42) *p*<0.001*	1.80 (1.39 , 2.33) *p*<0.001*	1.80 (1.39 , 2.33) *p*<0.001*	1.76 (1.35 , 2.29) *p*<0.001*	1.46 (1.11 , 1.91) *p*=0.007*	1.41 (1.07 , 1.86) *p*=0.016*
Inattention *(n=576)*	1.80 (1.40 , 2.32) *p*<0.001*	1.74 (1.35 , 2.25) *p*<0.001*	1.75 (1.36 , 2.26) *p*<0.001*	1.73 (1.34 , 2.24) *p*<0.001*	1.33 (1.01 , 1.77) *p*=0.044*	1.24 (0.92 , 1.67) *p*=0.152
Disorganised thinking *(n=563)*	2.06 (1.59 , 2.67) *p*<0.001*	1.97 (1.51 , 2.55) *p*<0.001*	2.01 (1.54 , 2.54) *p*<0.001*	1.94 (1,48 , 2.54) *p*<0.001*	1.52 (1.14 , 2.04) *p*=0.005*	1.42 (1.05 , 1.92) *p*=0.024*
Altered level of consciousness *(n=588)*	2.04 (1.58 , 2.63) *p*<0.001*	1.95 (1.50 , 2.52) *p*<0.001*	1.96 (1.51 , 2.53) *p*<0.001*	1.82 (1.40 , 2.37) *p*<0.001*	1.41 (1.06 , 1.88) *p*=0.018*	1.33 (0.98 , 1.79) *p*=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.*

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.

Figure 1: Study flowchart

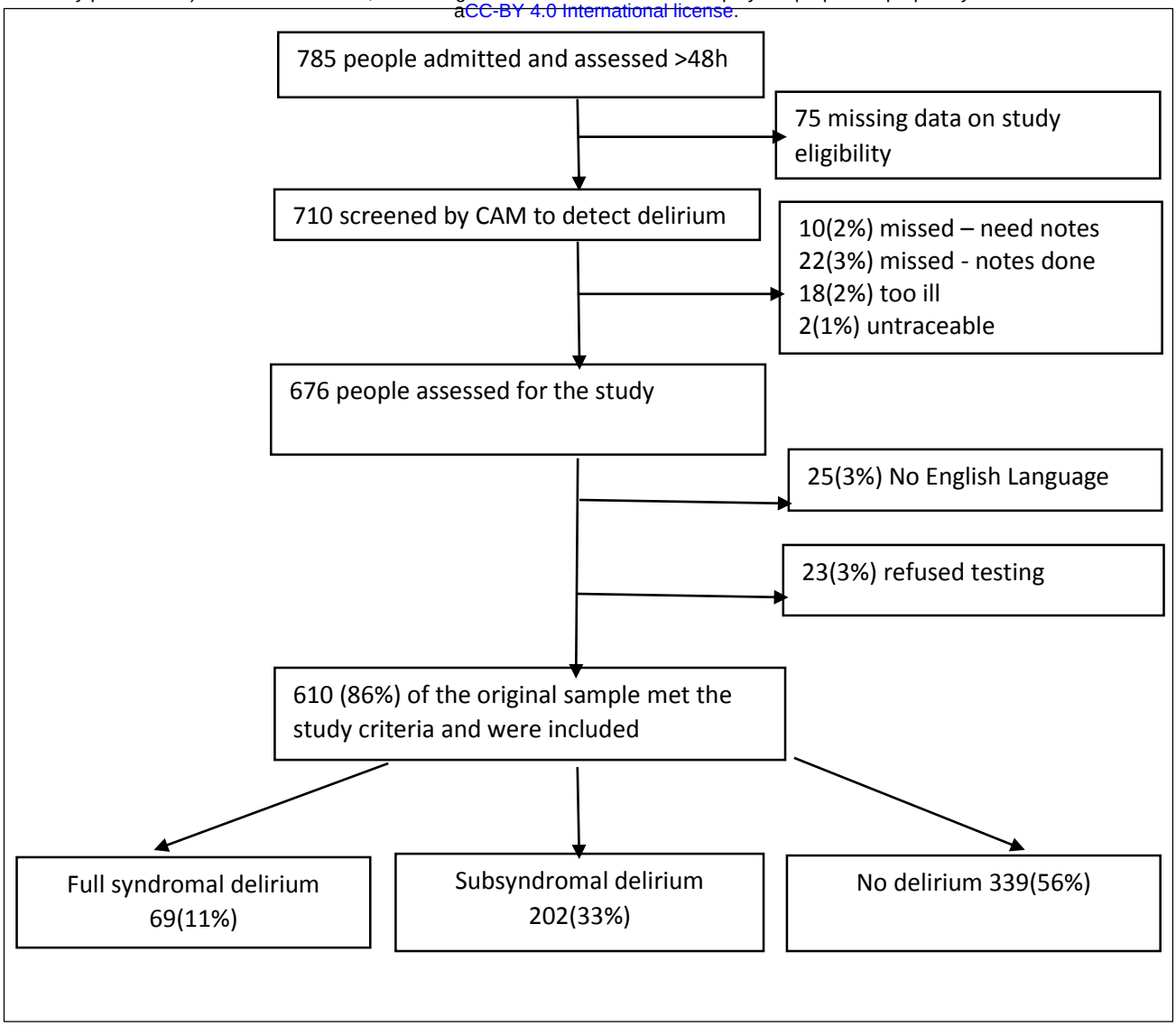

Figure 2: Kaplan Meier curves unadjusted survival estimates by delirium status

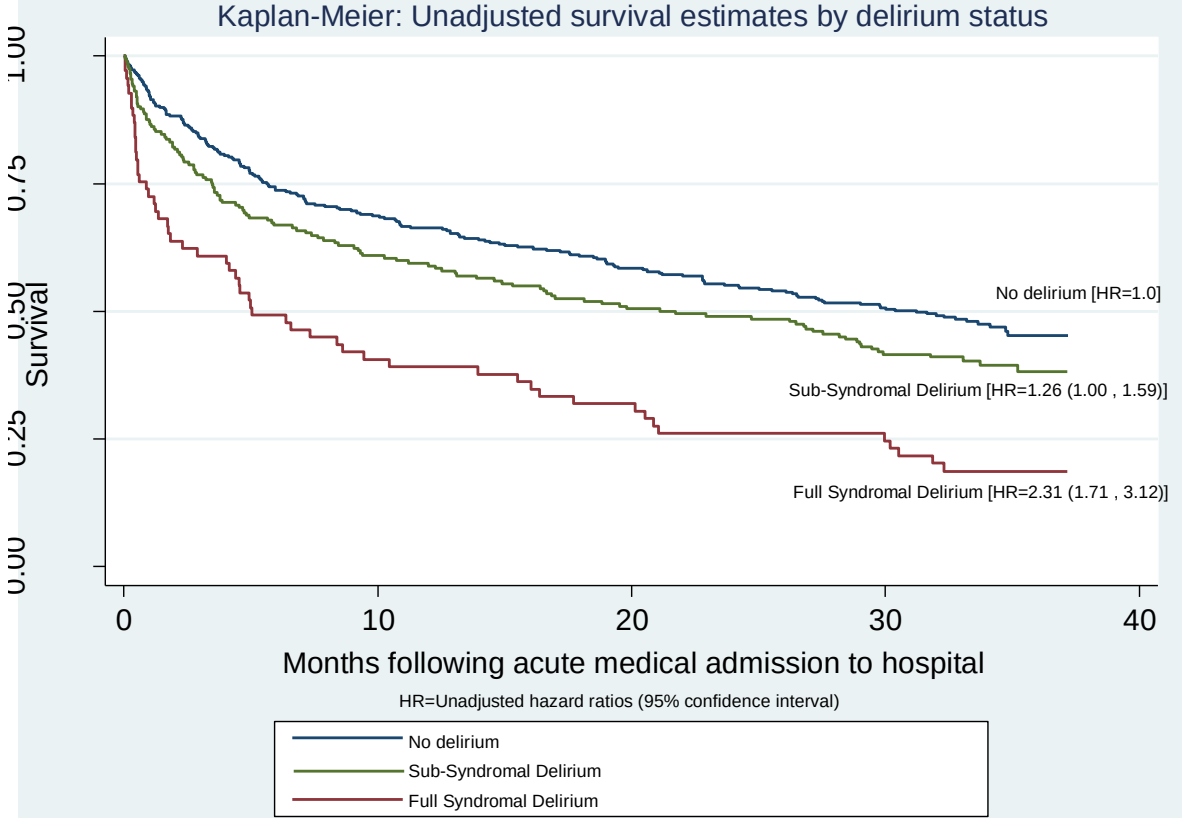

Figure 2: Kaplan Meier curves unadjusted survival estimates by delirium status