Published in final edited form as:

Am J Geriatr Psychiatry. 2017 March ; 25(3): 233–242. doi:10.1016/j.jagp.2016.05.016.

Exploring Delirium's Heterogeneity: Association between Arousal Subtypes at Initial Presentation and 6-month Mortality in Older Emergency Department Patients

Jin H. Han, MD, MSc^{1,2,9}, Nathan E. Brummel, MD, MSCI^{1,3,9}, Rameela Chandrasekhar, PhD⁷, Jo Ellen Wilson, MD⁸, Xulei Liu, MS⁷, Eduard E. Vasilevskis, MD, MPH^{1,5,9,10}, Timothy D. Girard, MD, MSCI^{1,3,9,10}, Maria E. Carlo, MD⁶, Robert S. Dittus, MD, MPH^{4,10}, John F. Schnelle, PhD^{1,4,6,10}, and E. Wesley Ely, MD, MPH^{1,3,9,10}

¹Center for Quality Aging, Vanderbilt University Medical Center, Nashville, TN

²Department of Emergency Medicine; Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

³Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN

⁴Division of General Internal Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN

⁵Section of Hospital Medicine, Vanderbilt University Medical Center, Nashville, TN

⁶Division of Geriatrics, Vanderbilt University Medical Center, Nashville, TN

⁷Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN

⁸Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN

⁹Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN

¹⁰Geriatric Research, Education, and Clinical Center, Department of Veterans Affairs Medical Center, Tennessee Valley Health Care Center, Nashville, TN

Abstract

Objectives—To determine how delirium subtyped by level of arousal at initial presentation affects 6-month mortality.

Send all correspondence to: Jin H. Han, MD, MSc, Vanderbilt University Medical Center, Department of Emergency Medicine, 703 Oxford House, Nashville, TN 37232-4700, Phone: 615-936-0087, Fax: 615-936-1316, jin.h.han@vanderbilt.edu, Twitter: @jinhanMD.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

This manuscript was a plenary oral presentation at the Society Academic Emergency Medicine Annual Meeting at San Diego, CA and was presented on May 13, 2015.

Disclosure

The authors have no conflicts of interest to disclose.

Design—This was a preplanned secondary analysis of two prospective cohort studies.

Setting—Academic tertiary care emergency department (ED).

Participants—1,084 ED patients who were 65 years old or older.

Measurements—At the time of enrollment, trained research personnel performed the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Richmond Agitation Sedation Scale (RASS) to determine delirium and level of arousal, respectively. Patients were categorized as having no delirium, delirium with normal arousal, delirium with decreased arousal, or delirium with increased arousal. Death was ascertained by medical record review and the Social Security Death Index. Cox proportional hazard regression was used to analyze the association between delirium arousal subtypes and 6-month mortality.

Results—Delirium with normal arousal was the only subtype that was significantly associated with increased 6-month mortality (HR=3.1, 95%CI: 1.3 – 7.4) compared with the no delirium group after adjusting for confounders. The HRs for delirium with decreased and increased arousal were 1.4 (95%CI: 0.9 – 2.1) and 1.3 (95%CI: 0.3 – 5.4), respectively.

Conclusion—Delirious ED patients with normal arousal at initial presentation had a three-fold increased hazard of death within 6-months compared to patients without delirium. There was a trend towards increased hazard of death in delirious ED patients with decreased arousal, but this relationship did not reach statistical significance. These data suggest that subtyping delirium by arousal may have prognostic value but requires confirmation with a larger study.

Keywords

Delirium; arousal; subtypes; mortality

Introduction

Delirium is a syndrome characterized by inattention accompanied by an acute loss of cognition. It affects 8 to 10% of older patients in the emergency department (ED)^{1–4} and 11 to 25% of older hospitalized patients^{5–10}, and it is a well-known predictor of mortality in multiple clinical settings.^{11–13}

Delirium is heterogeneous, both in etiology and in its clinical manifestations. The various phenotypes of delirium may be associated with outcomes in different ways. Elucidating the relationship between specific presentations of delirium and clinical outcomes could improve care delivery and improve the effectiveness of delirium interventions. Nevertheless, most delirium screening tools used currently in research and clinical practice dichotomize its diagnosis into presence or absence, making identification of potentially important subtypes difficult. The most commonly studied delirium subtype is based upon the patient's psychomotor activity (hypoactive, hyperactive, mixed, and none).^{14–18} Categorizing delirium by its psychomotor subtype is complex and is not standardized, which limits its reliability and clinical utility.^{19,20}

We propose a simple and standardized delirium subtyping method that is based upon just one component of delirium's psychomotor subtypes: level of arousal (consciousness). Level

of arousal is the patient's overall level of responsiveness to the environment and can be normal, decreased, or increased. Arousal is a component of many delirium assessments^{21–25} and has also been used as a delirium screen.^{26,27} Previous studies have also classified patients with decreased and normal arousal as having hypoactive delirium.^{2,28,29} It is possible, however, that delirious patients with normal arousal may represent its own distinct subtype. We sought to determine if the arousal subtype of delirium (normal, decreased, and increased) is associated with 6-month mortality compared with patients without delirium.

Methods

Study Design

This was a pre-planned secondary analysis of two prospective cohorts. The first cohort was designed to evaluate the relationship between delirium and patient outcomes and enrolled patients from May 2007 to August 2008 between 8AM and 10PM.^{12,30} The second cohort was used to validate three brief delirium assessments using a psychiatrist's assessment as the reference standard and enrolled patients from July 2009 to February 2012 between 8AM and 4PM.^{31,32} The local institutional review board approved these studies.

Setting and Participants

These studies were conducted in an urban ED located within an academic, tertiary care hospital with over 57,000 visits annually. Patients were included if they were 65 years of age or older and in the ED for less than 12 hours at the time of enrollment. The 12-hour cut-off was used to include patients who presented to the ED in the evening and early morning hours. Patients were excluded if they were previously enrolled, non-English speaking, persistently comatose, or were non-verbal and unable to follow simple commands prior to the acute illness as determined by proxy interview or medical record review. Patients who were initially comatose were re-evaluated 1 to 2 hours later;³³ those who remained comatose were excluded. Patients who were non-verbal and unable to follow simple commands prior to the acute illness were excluded because they were considered to have end-stage dementia. Delirium is difficult to diagnosis in this patient population even for a psychiatrist. Because the July 2009 to February 2012 cohort was designed to validate delirium assessments with auditory and visual components, patients were also excluded if they were deaf or blind.

Methods of Measurement

Delirium was assessed at the time of enrollment using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).²² The CAM-ICU uses the Confusion Assessment Method algorithm developed by Inouye et al.,²¹ which contains four features: altered mental status or fluctuating course, inattention, disorganized thinking, and altered level of consciousness (arousal). The CAM-ICU, however, incorporates objective assessments with pre-specified cutoffs to identify inattention and disorganized thinking. We chose to use the CAM-ICU because of its brevity (~1 minute), which made it an ideal assessment for the busy ED environment where interruptions frequently occur. At the time the first study was initiated, no other brief delirium assessments existed. In older ED patients, the CAM-ICU is 68% to 72% sensitive and 98.7% specific for delirium compared with an expert

psychiatrist's assessment and has excellent interrater reliability between research assistants and physicians ($\kappa = 0.92$).³⁴

As part of the CAM-ICU, the Richmond Agitation Scale (RASS) was also recorded to quantify level of arousal.^{28,29} The RASS ranges from -5 (coma) to +4 (combative); RASS of 0 represent normal level of arousal (alert and calm), a RASS < 0 represents decreased arousal, and a RASS > 0 represents increased arousal.³⁵ A patient with a RASS other than 0 was considered to have an altered level of consciousness. The RASS' weighted kappa was 0.63 between a research assistant and physician indicating very good inter-rater reliability.³⁶

Post-hoc, patients were categorized as having (a) no delirium (CAM-ICU negative), (b) delirium with decreased arousal (CAM-ICU positive, RASS<0), (c) delirium with increased arousal (CAM-ICU positive, RASS >0), or (d) delirium with normal arousal (CAM-ICU positive, RASS = 0).

Primary Outcome

To determine vital status of enrolled patients within 6 months of the index ED visit we: (i) Searched the electronic medical record, and those who had a documented ED visit, outpatient clinic visit, or hospitalization 6 months or more after study enrollment were considered to be alive. (ii) For those patients who could not be confirmed alive using the medical record, we searched the Social Security Death Index (SSDI) to determine dates of death. (iii) Finally, those patients without a death date recorded in the SSDI one year after the index visit were considered to be alive at 6 months. The SSDI is 88.2% sensitive for death in the general US population,³⁷ but its sensitivity improves in older patients and those born in the United States who are the majority of our patient population.³⁷ Of the 1,084 patients enrolled, 931 (85.9%) had a recorded death in the medical record or SSDI, or had an emergency department or hospital visit documented in their record 6 months after the index visit.

Additional Variables Collected

Patients were classified as having dementia if they had: (i) documented dementia in the medical record, (ii) a short form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score greater than 3.38,³⁸ or (iii) prescribed cholinesterase inhibitors prior to the ED visit. The Katz ADL Activities of Daily Living (Katz ADL) was used to ascertain baseline functional status (prior to the acute illness) and ranged from 0 (completely dependent) to 6 (completely independent).³⁹ Those with a score less than or equal to 4 were considered to be functionally dependent. Both the IQCODE and Katz ADL were prospectively collected in the ED at the time of enrollment.

Comorbidity burden was determined by the Charlson Comorbidity Index.⁴⁰ Severity of illness was quantified using a modified Acute Physiology Score (APS) of the Acute Physiology and Chronic Health Evaluation (APACHE) II score.⁴¹ The Glasgow coma scale was not incorporated in the APS because level of arousal was measured by the RASS and incorporated into the primary independent variable (delirium arousal subtype). Home benzodiazepine and opioid medication used at home and benzodiazepines and opioids given in the prehospital and ED were also recorded. The Charlson Comorbidity Index, APS, and

benzodiazepine and opioid medication administration in the home, prehospital, and ED settings were collected after patient enrollment using the electronic medical record.

Statistical Analysis

Measures of central tendency and dispersion for continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as frequency (percentage). Person-time was computed from the date of the index ED visit to date of death or end of follow-up, whichever came first. The product limit method of Kaplan and Meier were used to estimate crude 6-month mortality for delirium and its arousal subtypes. Cox proportional hazard regression was performed to determine if delirium and its arousal subtypes (using non-delirious patients as the reference group) were independently associated with 6-month mortality after adjusting for age, gender, comorbidity burden, severity of illness, dementia, functional dependence, and admission status. We selected covariates a priori based upon expert opinion within our research group and literature review.^{5,11–13,42,43} We chose covariates that were biologically plausible and likely confounded the relationship between 6-month mortality and the delirium arousal subtypes. We limited the number of covariates to one degree of freedom for every 15 deaths to minimize overfitting.⁴⁴ Hazard ratios (HRs) with their 95% confidence intervals (95% CIs) were reported.

The proportion of non-white patients, the proportion of those taking home benzodiazepine/opioid medications, and the proportion of those who received benzodiazepine/opioid medications in the ED or prehospital setting were markedly different between the various delirium arousal subtype groups. Therefore, we performed a post-hoc sensitivity analyses, adding nonwhite race, home benzodiazepine/opioid medications use, and administration of benzodiazepine/opioid medications in the ED or prehospital setting to the model.

We used multiple imputation to account for missing Katz ADL data in 19 patients (1.8%).⁴⁵ We assessed the proportional hazards assumption using log-log plots. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.0.1 (<http://www.r-project.org/>).

Results

Of the 1,903 patients who were screened, 1,084 patients met enrollment criteria (Figure 1). The cohort's characteristics can be seen in Table 2. At study enrollment, 155 patients (14.3%) were delirious as determined by the CAM-ICU and 140 patients died within 6-months (12.9%). The Kaplan-Meier survival curves for delirious and non-delirious ED patients can be seen in Figure 2a; the survival curve declined more slowly in patients without delirium compared to those with delirium. After adjusting for age, comorbidity burden, severity of illness, dementia, functional dependence, and admission status, the relationship between delirium in the ED and 6-month mortality persisted (HR = 1.49, 95% CI: 1.00 to 2.23).

Of the 155 delirious older ED patients, 132 (85.2%) were delirious with decreased arousal, 8 (5.2%) were delirious with increased arousal, and 15 (9.7%) were delirious with normal arousal. The Kaplan-Meier survival curves for each delirium arousal subtype can be seen

Figure 2b; those with normal arousal had the worst 6-month survival, with the majority of deaths occurring within 30 days of the index ED visit. After adjusting for age, comorbidity burden, severity of illness, dementia, functional dependence, and admission status, patients who had delirium with normal arousal had a three-fold increased hazard of death by 6 months compared with patients without delirium (Table 3). There was a trend towards increased hazard of death in delirious ED patients with decreased arousal, but this relationship did not reach statistical significance (Table 3). Finally, delirium with increased arousal was not significantly associated with increased 6-month mortality (Table 3).

Sensitivity analyses adjusting for nonwhite race, home benzodiazepine/opioid use, and benzodiazepine/opioid medication administration in the prehospital or ED setting did not change the HRs for each of the delirium arousal subtypes (Table 3).

Discussion

In our cohort of 1,084 acutely ill older ED patients, delirium presenting with normal arousal was independently associated with a three-fold increased hazard of death in the following 6 months compared to no delirium. Delirium presenting with decreased arousal was marginally associated with increased 6-month mortality. Our findings suggest that the current clinical and research methods of dichotomizing delirium as present or absent may be an oversimplification given that arousal-based subtypes have prognostic significance. Our data show that arousal-based subtypes can be easily measured and that classifying delirium by its arousal subtype would be feasible in busy clinical environments such as the ED.

Traditionally, delirium has been subtyped by psychomotor activity and prior studies have evaluated its role in outcomes, with mixed results. In the post-acute care and palliative care settings, hypoactive delirium was significantly associated with 1-year mortality.^{46,47} In patients with hip-fracture, however, hypoactive delirium had a protective effect on mortality.⁴⁸ Such discordant observations may be related to the patient populations studied or the method of psychomotor subtype determination.

Subtyping delirium by arousal may be a more efficient and simpler method to identify those at highest risk for adverse outcomes for non-psychiatrists. While decreased arousal is a characteristic of hypoactive delirium and increased arousal is a characteristic of hyperactive delirium, there is overlap. It is unclear how delirium with normal level of arousal corresponds to each psychomotor subtype. While these patients likely represent delirium with no psychomotor abnormalities, which can occur 24% to 35% of the cases,^{16,17} it is possible that a significant proportion may have hypoactive, hyperactive, or mixed-type delirium. Further study is needed to investigate the relationship between arousal and the psychomotor subtype and if one method of delirium subtyping is superior to the other with regard to determining prognosis.

Subtyping delirium by arousal subtypes may also have important clinical ramifications for patients who present with delirium in the acute care setting. While all patients with delirium should undergo a comprehensive diagnostic evaluation, health care providers may need to have heightened concern for a life-threatening illness in delirious patients with normal

arousal. Our findings may also have the potential to alter the paradigm in which delirium is managed. Current delirium management protocols are more effective at preventing delirium than they are at treating it. Most of these studies, however, have dichotomized delirium regardless of subtype. Thus, focusing these resource-intensive interventions on patients with delirium who present with normal arousal (and have worse outcomes) may be one way to improve mortality in this high-risk subtype. This approach would be analogous to what has taken place in acute coronary syndromes. Only patients with ST-segment elevation myocardial infarction receive and benefit from urgent revascularization.^{49,50}

While this hypothesis generating secondary analysis identified a potentially important and easily identifiable group of patients with delirium presenting with normal arousal who had an increased risk of death, additional study is also needed to fully clarify the clinical utility of subtyping delirium by level of arousal. First, the mechanisms for the association between delirium with normal arousal and 6-month mortality need to be elucidated. The poor prognosis may be related to delirium etiology, delirium severity or different underlying pathogenic mechanisms. Future studies should capture etiologic, delirium severity, and biomarker data. Second, we assessed for delirium and arousal at initial presentation. Thus, given delirium's fluctuating nature, it is possible that delirious patients with normal arousal may have transitioned to abnormal arousal and patients with abnormal arousal may have transitioned into normal arousal. Delirious patients may have also transitioned to a non-delirious state and non-delirious patients may have transitioned into a delirious state. Future studies should examine how the duration of each delirium arousal subtype and transitions between delirium and level of arousal states affect outcomes. Third, future studies should investigate how delirium's arousal subtypes affect long-term cognitive and functional decline which are critical components to the older patient's quality of life. Lastly, several studies have reported that impaired arousal, irrespective of delirium status, is associated with prolonged hospitalizations, increased risk of being discharged to a skilled nursing facility, and higher 6-month mortality.^{43,51,52} In addition to the delirium arousal subtypes reported in our study, future studies should also analyze non-delirious patients by level of arousal to elucidate how arousal states in both delirious and non-delirious patients impact outcomes.

Limitations

This was a secondary analysis and requires confirmation. This was a single-center study and our findings may not be generalizable to other settings. The number delirious patients with normal arousal and increased arousal were relatively small and consequently, the 95%CI for each delirium arousal subtype's HR overlapped. We were unable to state that one delirium arousal subtype had more prognostic value over the other with any statistical certainty. Our study requires confirmation with a larger number of delirious patients enrolled from multiple centers. We used the CAM-ICU to detect delirium. Prior studies have shown a 30% false negative rate in older ED patients. Based upon a previous validation study that enrolled 50 psychiatrist-diagnosed delirious patients,³⁴ we observed that patients with false-negative CAM-ICUs were less likely to have baseline dementia, had subtler impairments in cognition, and were slightly more likely to have a normal RASS (Supplemental Table 1). These missed cases of delirium could have biased our findings in either direction (null or increased the HR). The CAM-ICU, however, possesses excellent specificity and therefore it

is unlikely that we categorized patients with delirium who were not. While the RASS' kappa is 0.63 (indicating very good interobserver reliability),³⁶ misclassification of the arousal subtype may have still occurred. Inherent to any prospective cohort study is residual confounding. Because global tests of cognition do not accurately reflect baseline cognition in delirious patients, we relied upon the IQCODE which is an informant based dementia screen. The IQCODE is a relatively crude measure of dementia and does not assess for dementia severity, and may have also further contributed to residual confounding. Aside from psychoactive medication administration in the prehospital or ED setting, we also did not adjust for other treatments administered in the ED.

Conclusions

Patients with delirium who presented with normal arousal at initial presentation in the ED had a three-fold increased hazard of death within 6-months compared to patients without delirium. There was a trend towards increased hazard of death in delirious ED patients with decreased arousal, but this relationship did not reach statistical significance. These data suggest that subtyping delirium by arousal may have prognostic value. Future studies are needed to confirm these findings and investigate how delirium's arousal and psychomotor subtypes are related to each other.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by the Vanderbilt Physician Scientist Development Award, Emergency Medicine Foundation, and National Institute on Aging of the National Institutes of Health under award number K23AG032355. This study was also supported by the National Center for Research Resources, Grant UL1 RR024975-01, and is now at the National Center for Advancing Translational Sciences, Grant 2 UL1 TR000445-06. Dr. Brummel was supported by the National Institutes on Health under awards R03AG040549 and KL2TR000446 and by the Vanderbilt Clinical and Translational Scholars Program. Dr. Vasilevskis was supported in part by the National Institute on Aging of the National Institutes of Health under award number K23AG040157. Dr. Girard received support from the National Institute of Health (AG034257 and AG035117). Dr. Ely was supported in part by the National Institute on Aging of the National Institutes of Health under award numbers R01AG027472 and R01AG035117, and a Veteran Affairs MERIT award. Drs. Vasilevskis, Girard, Schnelle, Dittus, and Ely were supported by the Veteran Affairs Geriatric Research, Education, and Clinical Center (GRECC). The content is solely the responsibility of the authors and does not necessarily represent the official views of Vanderbilt University Medical Center, Emergency Medicine Foundation, National Institutes of Health, and Veterans Affairs.

References

1. Hustey FM, Meldon SW, Smith MD, et al. The effect of mental status screening on the care of elderly emergency department patients. *Ann Emerg Med.* 2003; 41:678–684. [PubMed: 12712035]
2. Han JH, Zimmerman EE, Cutler N, et al. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. *Acad Emerg Med.* 2009; 16:193–200. [PubMed: 19154565]
3. Elie M, Rousseau F, Cole M, et al. Prevalence and detection of delirium in elderly emergency department patients. *CMAJ.* 2000; 163:977–981. [PubMed: 11068569]
4. Kakuma R, du Fort GG, Arsenault L, et al. Delirium in older emergency department patients discharged home: effect on survival. *J Am Geriatr Soc.* 2003; 51:443–450. [PubMed: 12657062]

5. Inouye SK, Rushing JT, Foreman MD, et al. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. *J Gen Intern Med*. 1998; 13:234–242. [PubMed: 9565386]
6. Levkoff SE, Evans DA, Liptzin B, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med*. 1992; 152:334–340. [PubMed: 1739363]
7. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *JAMA*. 1990; 263:1097–1101. [PubMed: 2299782]
8. Pompei P, Foreman M, Cassel CK, et al. Detecting delirium among hospitalized older patients. *Arch Intern Med*. 1995; 155:301–307. [PubMed: 7832602]
9. O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc*. 1997; 45:174–178. [PubMed: 9033515]
10. Pitkala KH, Laurila JV, Strandberg TE, et al. Prognostic significance of delirium in frail older people. *Dement Geriatr Cogn Disord*. 2005; 19:158–163. [PubMed: 15627764]
11. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004; 291:1753–1762. [PubMed: 15082703]
12. Han JH, Shintani A, Eden S, et al. Delirium in the emergency department: an independent predictor of death within 6 months. *Ann Emerg Med*. 2010; 56:244–252. [PubMed: 20363527]
13. McCusker J, Cole M, Abrahamowicz M, et al. Delirium predicts 12-month mortality. *Arch Intern Med*. 2002; 162:457–463. [PubMed: 11863480]
14. de Rooij SE, Schuurmans MJ, van der Mast RC, et al. Clinical subtypes of delirium and their relevance for daily clinical practice: a systematic review. *Int J Geriatr Psychiatry*. 2005; 20:609–615. [PubMed: 16021665]
15. Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. *Semin Clin Neuropsychiatry*. 2000; 5:75–85. [PubMed: 10837096]
16. Godfrey A, Leonard M, Donnelly S, et al. Validating a new clinical subtyping scheme for delirium with electronic motion analysis. *Psychiatry Res*. 2010; 178:186–190. [PubMed: 20452050]
17. Meagher D, Adamis D, Leonard M, et al. Development of an abbreviated version of the Delirium Motor Subtyping Scale (DMSS-4). *Int Psychogeriatr*. 2014:1–10.
18. Meagher DJ, Leonard M, Donnelly S, et al. A longitudinal study of motor subtypes in delirium: frequency and stability during episodes. *J Psychosom Res*. 2012; 72:236–241. [PubMed: 22325705]
19. Meagher DJ, Moran M, Raju B, et al. Motor symptoms in 100 patients with delirium versus control subjects: comparison of subtyping methods. *Psychosomatics*. 2008; 49:300–308. [PubMed: 18621935]
20. Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. *Palliat Support Care*. 2004; 2:171–179. [PubMed: 16594247]
21. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990; 113:941–948. [PubMed: 2240918]
22. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001; 286:2703–2710. [PubMed: 11730446]
23. Han JH, Wilson A, Vasilevskis EE, et al. Diagnosing delirium in older emergency department patients: validity and reliability of the delirium triage screen and the brief confusion assessment method. *Ann Emerg Med*. 2013; 62:457–465. [PubMed: 23916018]
24. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: Derivation and Validation of a 3-Minute Diagnostic Interview for CAM-Defined Delirium: A Cross-sectional Diagnostic Test Study. *Ann Intern Med*. 2014; 161:554–561. [PubMed: 25329203]
25. Bellelli G, Morandi A, Davis DH, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing*. 2014; 43:496–502. [PubMed: 24590568]
26. Chester JG, Beth Harrington M, Rudolph JL, et al. Serial administration of a modified Richmond Agitation and Sedation Scale for delirium screening. *J Hosp Med*. 2012; 7:450–453. [PubMed: 22173963]

27. Tieges Z, McGrath A, Hall RJ, et al. Abnormal level of arousal as a predictor of delirium and inattention: an exploratory study. *Am J Geriatr Psychiatry*. 2013; 21:1244–1253. [PubMed: 24080383]
28. Pandharipande P, Cotton BA, Shintani A, et al. Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients. *Intensive Care Med*. 2007; 33:1726–1731. [PubMed: 17549455]
29. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc*. 2006; 54:479–484. [PubMed: 16551316]
30. Han JH, Eden S, Shintani A, et al. Delirium in older emergency department patients is an independent predictor of hospital length of stay. *Acad Emerg Med*. 2011; 18:451–457. [PubMed: 21521405]
31. Han JH, Wilson A, Graves AJ, et al. Validation of the Confusion Assessment Method for the Intensive Care Unit in Older Emergency Department Patients. *Acad Emerg Med*. 2013 (In press).
32. Han JH, Wilson A, Vasilevskis EE, et al. Diagnosing Delirium in Older Emergency Department Patients: Validity and Reliability of the Delirium Triage Screen and the Brief Confusion Assessment Method. *Ann Emerg Med*. 2013 (In press).
33. Association ED. Society AD The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. *BMC Med*. 2014; 12:141. [PubMed: 25300023]
34. Han JH, Wilson A, Graves AJ, et al. Validation of the Confusion Assessment Method for the Intensive Care Unit in older emergency department patients. *Acad Emerg Med*. 2014; 21:180–187. [PubMed: 24673674]
35. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003; 289:2983–2991. [PubMed: 12799407]
36. Han JH, Vasilevskis EE, Schnelle JF, et al. The Diagnostic Performance of the Richmond Agitation Sedation Scale for Detecting Delirium in Older Emergency Department Patients. *Acad Emerg Med*. 2015; 22:878–882. [PubMed: 26113020]
37. Schisterman EF, Whitcomb BW. Use of the Social Security Administration Death Master File for ascertainment of mortality status. *Popul Health Metr*. 2004; 2:2. [PubMed: 15003125]
38. Holsinger T, Deveau J, Boustani M, et al. Does this patient have dementia? *JAMA*. 2007; 297:2391–2404. [PubMed: 17551132]
39. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc*. 1983; 31:721–727. [PubMed: 6418786]
40. Murray SB, Bates DW, Ngo L, et al. Charlson Index is associated with one-year mortality in emergency department patients with suspected infection. *Acad Emerg Med*. 2006; 13:530–536. [PubMed: 16551775]
41. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985; 13:818–829. [PubMed: 3928249]
42. Elie M, Cole MG, Primeau FJ, et al. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med*. 1998; 13:204–212. [PubMed: 9541379]
43. Han JH, Vasilevskis EE, Shintani A, et al. Impaired arousal at initial presentation predicts 6-month mortality: an analysis of 1084 acutely ill older patients. *J Hosp Med*. 2014; 9:772–778. [PubMed: 25352356]
44. Harrell, FE. Regression modeling strategies : with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001.
45. Allison, PD. Imputation of categorical variables with PROC MI; Presented at 30th Meeting of SAS. User Group International; April 10–13, (2005); Philadelphia, PA.
46. Meagher DJ, Leonard M, Donnelly S, et al. A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis. *J Psychosom Res*. 2011; 71:395–403. [PubMed: 22118382]
47. Kiely DK, Jones RN, Bergmann MA, et al. Association between psychomotor activity delirium subtypes and mortality among newly admitted post-acute facility patients. *J Gerontol A Biol Sci Med Sci*. 2007; 62:174–179. [PubMed: 17339642]

48. Marcantonio E, Ta T, Duthie E, et al. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. *J Am Geriatr Soc.* 2002; 50:850–857. [PubMed: 12028171]
49. De Luca G, van 't Hof AW, de Boer MJ, et al. Time-to-treatment significantly affects the extent of ST-segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty. *Eur Heart J.* 2004; 25:1009–1013. [PubMed: 15191770]
50. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *N Engl J Med.* 2001; 345:1368–1377. [PubMed: 11794169]
51. Yevchak AM, Doherty K, Archambault EG, et al. The association between an ultrabrief cognitive screening in older adults and hospital outcomes. *J Hosp Med.* 2015; 10:651–657. [PubMed: 26374602]
52. Yevchak AM, Han JH, Doherty K, et al. Impaired Arousal in Older Adults Is Associated With Prolonged Hospital Stay and Discharge to Skilled Nursing Facility. *J Am Med Dir Assoc.* 2015

Figure 1.
Enrollment flow diagram

Figure 2.

a. Kaplan-Meier survival curves for 1,084 acutely ill patients according to delirium status. The dashed line represents those who were delirious in the ED and the solid line represents those who were not delirious. Log-rank test p-value was less than 0.001. Cox proportional hazard regression was performed adjusting for age, gender, comorbidity burden, severity of illness, dementia, functional dependence, and admission status. Delirium in the ED was significantly associated with 6-month mortality (HR = 1.49, 95% CI: 1.00 to 2.23) compared with the no delirium group after adjusting for confounders. **b.** Kaplan-Meier survival curves

for 1,084 acutely ill patients according to delirium arousal subtype. Log-rank test p-value was less than 0.001. Cox proportional hazard regression was performed adjusting for age, gender, comorbidity burden, severity of illness, dementia, functional dependence, and admission status. Delirium with normal arousal was the only subtype that was significantly associated with 6-month mortality (HR=3.1, 95% CI: 1.3 – 7.4) compared with the no delirium group after adjusting for confounders. The HRs for the delirium with decreased and increased arousal were 1.4 (95% CI: 0.9 – 2.1) and 1.3 (95% CI: 0.3 – 5.4), respectively.

Table 1**Patient Characteristics**

Patient characteristics and demographics of enrolled patients. Continuous and ordinal variables are expressed in medians and interquartile (IQR) ranges. Categorical variables are expressed as frequency (percentage).

	No Delirium n=929	All Delirium n=155	Delirium/ Normal Arousal n=15	Delirium/ Decreased Arousal n=132	Delirium/ Increased Arousal n=8
Median age (IQR)	74 (69, 80)	77 (71, 84)	74 (68, 81)	77.5 (71, 84)	74.5 (70.5, 76.5)
Female gender	499 (53.7%)	92 (59.4%)	8 (53.3%)	81 (61.4%)	3 (37.5%)
Non-white race	137 (14.8%)	36 (23.2%)	1 (6.7%)	30 (22.7%)	5 (62.5%)
Residence					
Home Alone	232 (25.0%)	20 (12.9%)	2 (13.3%)	18 (13.6%)	0 (0.0%)
Home with Others	607 (65.3%)	97 (62.6%)	5 (33.3%)	88 (66.7%)	4 (50.0%)
Assisted living	34 (3.7%)	8 (5.2%)	1 (6.7%)	7 (5.3%)	0 (0.0%)
Rehabilitation	10 (76.9%)	3 (1.9%)	0 (0.0%)	3 (2.3%)	0 (0.0%)
Nursing home	42 (4.5%)	27 (17.4%)	7 (46.7%)	16 (23.1%)	4 (50%)
Dementia *	203 (21.9%)	91 (58.7%)	9 (60.0%)	76 (57.6%)	6 (75.0%)
Dependent †	148 (15.9%)	71 (45.8%)	6 (40.0%)	61 (46.2%)	4 (50.0%)
Median Charlson (IQR) ‡	2 (1, 4)	3 (2, 5)	4 (2, 4)	3 (2, 6)	3.5 (2.5, 4.0)
Median APS (IQR) §	2 (1, 4)	3 (2, 6)	2 (2, 5)	3 (2, 6)	4 (2.5, 6.5)
Primary complaint					
Abdominal pain	49 (5.3%)	9 (5.8%)	1 (6.7%)	7 (5.3%)	1 (12.5%)
Altered mental status	13 (1.4%)	35 (22.6%)	5 (33.3%)	28 (21.2%)	2 (25.0%)
Chest pain	145 (15.6%)	14 (9.0%)	1 (6.7%)	12 (9.1%)	1 (12.5%)
General weakness	78 (8.4%)	19 (12.3%)	2 (13.3%)	17 (12.9%)	0 (0.0%)
Shortness of breath	95 (10.2%)	10 (6.4%)	0 (0.0%)	10 (7.6%)	0 (0.0%)
Syncope	51 (5.5%)	5 (3.2%)	0 (0.0%)	4 (3.0%)	1 (12.5%)

	No Delirium n=929	All Delirium n=155	Delirium/ Normal Arousal n=15	Delirium/ Decreased Arousal n=132	Delirium/ Increased Arousal n=8
Other	498 (53.6%)	63 (40.7%)	6 (40.0%)	54 (40.9%)	3 (37.5%)
Home benzodiazepines or opioid medications use	348 (37.5%)	79 (51.0%)	10 (66.7%)	62 (47.0%)	7 (87.5%)
Benzodiazepines or opioid medications administration in emergency department or pre-hospital setting	221 (23.8%)	34 (21.9%)	1 (6.7%)	32 (24.2%)	1 (12.5%)
Admitted to hospital	549 (59.1%)	120 (77.4%)	13 (86.7%)	101 (76.5%)	6 (75.0%)
Death within 6-months	97 (10.4%)	43 (27.7%)	6 (40.0%)	35 (26.5%)	2 (25.0%)

* Patient was considered to have dementia if it was documented in the medical record, the patient was on home cholinesterase inhibitors, or had a short form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) greater than 3.38.

[†] Patients with a Katz Activities of Daily Living were less than 5 were considered to be functionally dependent. There were 19 patients with missing Katz Activities of Daily Living.

[‡] Charlson index is a weighted scale used to measure comorbidity burden. Higher scores indicate higher comorbidity burden.

[§] The Acute Physiology Score (APS) of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was used to quantify severity of illness. Glasgow Coma Scale was not incorporated in this score. Higher scores indicated higher severities of illness.

Table 2

Independent associations between delirium arousal subtypes and 6-month mortality.

CAM-ICU / RASS Category	Main Model HR (95%CI)	Sensitivity Analysis Model HR (95%CI)
Delirium with normal arousal	3.1 (1.3 – 7.4)	2.9 (1.2 – 6.8)
Delirium with decreased arousal	1.4 (0.9 – 2.1)	1.5 (1.0 – 2.4)
Delirium with increased arousal	1.3 (0.3 – 5.4)	1.7 (0.4 – 7.4)
No Delirium	Reference	Reference

Delirium was determined by the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and its arousal subtypes was determined by the Richmond Agitation Sedation Scale (RASS). The model was adjusted for age, gender, comorbidity burden, severity of illness, dementia, functional dependence, and admission status. For the sensitivity analysis, non-white race, home benzodiazepine/opioid medication use, and benzodiazepine/opioid medication administration in the prehospital or emergency department settings were added to the main model.