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ORIGINAL RESEARCH

Impaired Arousal at Initial Presentation Predicts 6-Month Mortality: An Analysis of 1084 Acutely Ill Older Patients

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OBJECTIVES: Impaired arousal signifies underlying brain dysfunction, but its clinical significance outside the intensive care unit remains unclear. We sought to determine if impaired arousal at initial presentation was associated with higher 6-month mortality and if this relationship existed in the absence of delirium.

DESIGN: Prospective cohort study.

SETTING: An emergency department located within an academic, tertiary care hospital.

PARTICIPANTS: A total of 1084 noncomatose patients who were aged 65 years or older.

MEASUREMENTS: The Richmond Agitation-Sedation Scale (RASS) is a 10-second arousal scale; a score of 0 indicates normal arousal. Cox proportional hazard regression was performed adjusting for patient characteristics, admission status, and psychoactive medication administration. To determine if impaired arousal in the absence of delirium was associated with 6-month mortality, Cox proportional hazard regression was performed in a subset of 406 patients who received a psychiatric assessment; the inverse weighted propensity score method was used to minimize residual confounding. Hazard ratios (HR) with their 95% confidence intervals (95% CI) were reported.

RESULTS: Patients with impaired arousal were 73% more likely to die within 6 months (HR: 1.73, 95% CI: 1.21-2.49). Even in the absence of delirium, patients with an abnormal RASS were more likely to die within 6 months (HR: 2.20, 95% CI: 1.10-4.41).

CONCLUSION: Impaired arousal at initial presentation is an independent predictor of death within 6 months in a diverse group of acutely ill older patients, even in the absence of delirium. Routine RASS assessment of arousal during clinical care may be warranted as it correlates with prognosis. *Journal of Hospital Medicine* 2014;9:772–778. © 2014 Society of Hospital Medicine

Arousal is defined as the patient's overall level of responsiveness to the environment. Its assessment is standard of care in most intensive care units (ICUs) to monitor depth of sedation and underlying brain dysfunction. There has been recent interest in expanding the role of arousal assessment beyond the ICU. Specifically, the Veterans Affairs Delirium Working Group proposed that simple arousal assessment be a vital sign to quantify underlying brain dysfunction.[1] The rationale is that impaired arousal is closely linked with delirium,[2] and is an integral component of multiple delirium assessments.[3–5] Chester et al. observed that the presence of impaired arousal was 64% sensitive and 93% specific for delirium diagnosed by a psychiatrist.[2] Delirium is an under-recognized public health problem that affects up to 25% of older hospitalized patients,[6,7] is associated with a multitude of adverse outcomes such as death and accelerated cognitive decline,[8] and costs the US healthcare system an excess of $152 billion dollars.[9]

Most delirium assessments require the patient to undergo additional cognitive testing. The assessment of arousal, however, requires the rater to merely observe the patient during routine clinical care and can be easily integrated into the clinical workflow.[10] Because of its simplicity and brevity, assessing arousal alone using validated scales such as the Richmond Agitation-Sedation Scale (RASS) may be a more appealing alternative to traditional, more complex delirium screening in the acute care setting. Its clinical utility would be further strengthened if impaired arousal was also associated with mortality, and conferred risk even in the absence of delirium. As a result, we sought to determine if impaired arousal at initial

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presentation in older acutely ill patients predicted 6-month mortality and whether this relationship was present in the absence of delirium.

METHODS

Design Overview

We performed a planned secondary analysis of 2 prospective cohorts that enrolled patients from May 2007 to August 2008 between 8 AM and 10 PM during the weekdays, and July 2009 to February 2012 between 8 AM and 4 PM during the weekdays. The first cohort was designed to evaluate the relationship between delirium and patient outcomes.[11,12] The second cohort was used to validate brief delirium assessments using a psychiatrist's assessment as the reference standard.[5,13] The local institutional review board approved these studies.

Setting and Participants

These studies were conducted in an urban emergency department located within an academic, tertiary care hospital with over 57,000 visits annually. Patients were included if they were 65 years or older and in the emergency department for <12 hours at the time of enrollment. The 12-hour cutoff was used to include patients who presented to the emergency department in the evening and early morning hours. Patients were excluded if they were previously enrolled, non-English speaking, comatose, or were nonverbal and unable to follow simple commands prior to the acute illness. 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.

Measurement of Arousal

RASS is an arousal scale commonly used in ICUs to assess depth of sedation and ranges from −5 (unarousable) to +4 (combative); 0 represents normal arousal.[10,14] The RASS simply requires the rater to observe the patient during their routine interactions and does not require any additional cognitive testing. The RASS terms "sedation" was modified to "drowsy" (Table 1), because we wanted to capture impaired arousal regardless of sedation administration. We did not use the modified RASS (mRASS) proposed by the Veteran's Affairs Delirium Working Group, because it was published after data collection began.[1] The mRASS is very similar to the RASS, except it also incorporates a very informal inattention assessment. The RASS was ascertained by research assistants who were college students and graduates, and emergency medical technician basics and paramedics. The principal investigator gave them a 5-minute didactic lecture about the RASS and observed them perform the RASS in at least 5 patients prior to the start of the study. Inter-rater reliability between trained research assistants and a physician was assessed for 456 (42.0%) patients of the study sample. The weighted kappa of the RASS was 0.61, indicating very good inter-rater reliability. Because the 81.7% of patients with impaired arousal had a RASS of −1, the RASS dichotomized as normal (RASS = 0) or impaired (RASS other than 0).

TABLE 1. Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive
+2	Agitated	Frequent nonpurposeful movement
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
−1	Slight drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)
−2	Moderately drowsy	Briefly awakens with eye contact to voice (<10 seconds)
−3	Very drowsy	Movement or eye opening to voice (but no eye contact)
−4	Awakens to pain only	No response to voice, but movement or eye opening to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

NOTE: The Richmond Agitation-Sedation Scale (RASS) is a brief (<10 seconds) arousal scale that was developed by Sessler et al.[10] The RASS is traditionally used in the intensive care unit to monitor depth of sedation. The terms were modified to better reflect the patient's level of arousal rather than sedation. A RASS of 0 indicates normal level of arousal (awake and alert), whereas a RASS <0 indicates decreased arousal, and a RASS >0 indicates increased arousal.

Death Ascertainment

Death within 6 months was ascertained using the following algorithm: (1) The electronic medical record was searched to determine the patient's death status. (2) Patients who had a documented emergency department visit, outpatient clinic visit, or hospitalization after 6 months were considered to be alive at 6 months. (3) For the remaining patients, date of death was searched in the Social Security Death Index (SSDI). (4) Patients without a death recorded in the SSDI 1 year after the index visit was considered to be alive at 6 months. Nine hundred thirty-one (85.9%) out of 1084 patients 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 considered to have dementia if they had: (1) documented dementia in the medical record, (2) a short form Informant Questionnaire on Cognitive Decline in the Elderly score (IQCODE) greater than 3.38,[15] or (3) prescribed cholinesterase inhibitors prior to admission. The short form IQCODE is an informant questionnaire with 16 items; a cutoff of 3.38 out of 5.00 is 79% sensitive and 82% specific for dementia.[16] Premorbid functional status was determined by the Katz Activities of Daily Living (Katz ADL) and ranges from 0 (completely dependent) to 6 (completely independent).[17] Patients with a score <5 were considered to be functionally dependent. Both the IQCODE and Katz

ADL were prospectively collected in the emergency department at the time of enrollment.

The Charlson Comorbidity Index was used to measure comorbid burden.[18] The Acute Physiology Score (APS) of the Acute Physiology and Chronic Health Evaluation II score was used to quantify severity of illness.[19] The Glasgow Coma Scale was not included in the APS because it was not collected. Intravenous, intramuscular, and oral benzodiazepine and opioids given in the prehospital and emergency department were also recorded. The Charlson Comorbidity Index, APS, and benzodiazepine and opioid administration were collected after patient enrollment using the electronic medical record.

Within 3 hours of the RASS, a subset of 406 patients was evaluated by a consultation-liaison psychiatrist who determined the patient's delirium status using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria.[20] Details of their comprehensive assessments have been described in a previous report.[5]

Statistical Analysis

Measures of central tendency and dispersion for continuous variables were reported as medians and interquartile ranges. Categorical variables were reported as proportions. For simple comparisons, Wilcoxon rank sum tests were performed for continuous data, and χ^2 analyses or Fisher exact test were performed for categorical data. To evaluate the predictive validity of impaired arousal on 6-month mortality, the cumulative probability of survival was estimated within 6 months from the study enrollment date using the Kaplan-Meier method. Cox proportional hazards regression was performed to assess if impaired arousal was independently associated with 6-month mortality after adjusting for age, gender, nonwhite race, comorbidity burden (Charlson Comorbidity Index), severity of illness (APS), dementia, functional dependence (Katz ADL < 5), nursing home residence, admission status, and benzodiazepine or opioid medication administration. Patients were censored at the end of 6 months. The selection of covariates was based upon expert opinion and literature review. The number of covariates used for the model was limited by the number of events to minimize overfitting; 1 *df* was allowed for every 10 to 15 events.[21] Because severity of illness, psychoactive medication administration, and admission status might modify the relationship between 6-month mortality and impaired arousal, 2-way interaction terms were incorporated. To maintain parsimony and minimize overfitting and collinearity, nonsignificant interaction terms ($P > 0.20$) were removed in the final model.[22] Hazard ratios (HR) with their 95% confidence interval (95% CI) were reported.

To determine if arousal was associated with 6-month mortality in the absence of delirium, we performed another Cox proportional hazard regression in a subset of 406 patients who received a psychiatrist assessment. Six-month mortality was the dependent variable, and the independent variable was a 3-level categorical variable of different arousal/delirium combinations: (1) impaired arousal/delirium positive, (2) impaired arousal/delirium negative, and (3) normal arousal (with or without delirium). Because there were only 8 patients who had normal arousal with delirium, this group was collapsed into the normal arousal without delirium group. Because there were 55 deaths, the number of covariates that could be entered into the Cox proportional hazard regression model was limited. We used the inverse weighted propensity score method to help minimize residual confounding.[23] Traditional propensity score adjustment could not be performed because there were 3 arousal/delirium categories. Similar to propensity score adjustment, inverse weighted propensity score method was used to help balance the distribution of patient characteristics among the exposure groups and also allow adjustment for multiple confounders while minimizing the degrees of freedom expended. A propensity score was the probability of having a particular arousal/delirium category based upon baseline patient characteristics. Multinomial logistic regression was performed to calculate the propensity score, and the baseline covariates used were age, gender, nonwhite race, comorbidity burden, severity of illness, dementia, functional dependence, and nursing home residence. For the Cox proportional hazard regression model, each observation was weighted by the inverse of the propensity score for their given arousal/delirium category; propensity scores exceeding the 95th percentile were trimmed to avoid overly influential weighting. Benzodiazepine and opioid medications given in the emergency department and admission status were adjusted as covariates in the weighted Cox proportional hazard regression model.

Nineteen patients (1.8%) had missing Katz ADL; these missing values were imputed using multiple imputation. The reliability of the final regression models were internally validated using the bootstrap method.[21] Two thousand sets of bootstrap samples were generated by resampling the original data, and the optimism was estimated to determine the degree of overfitting.[21] An optimism value >0.85 indicated no evidence of substantial overfitting.[21] Variance inflation factors were used to check multicollinearity. Schoenfeld residuals were also analyzed to determine goodness-of-fit and assess for outliers. P values <0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and open source R statistical software version 3.0.1 (http://www.r-project.org/).

RESULTS

A total of 1903 patients were screened, and 1084 patients met enrollment criteria (Figure 1). Of these,

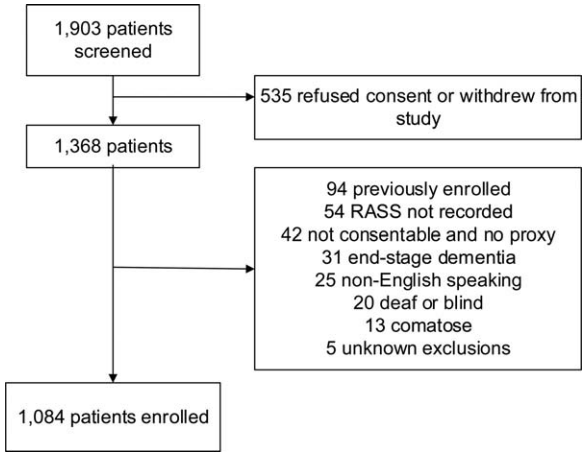

FIG. 1. Enrollment flow diagram. RASS, Richmond Agitation-Sedation Scale. Patients who were non-verbal or unable to follow simple commands prior to their acute illness were considered to have end-stage dementia.

1051 (97.0%) were non-ICU patients. Patient characteristics of this cohort can be seen in Table 2. Enrolled patients and potentially eligible patients who presented to the emergency department during the enrollment window were similar in age, gender, and severity of illness, but enrolled patients were slightly more likely to have a chief complaint of chest pain and syncope (unpublished data).

Of those enrolled, 249 (23.0%) had an abnormal RASS at initial presentation, and their distribution can be seen in Figure 2. Within 6 months, patients with an abnormal RASS were more likely to die compared with patients with a RASS of 0 (23.7% vs 9.7%, $P < 0.001$). The Kaplan-Meier survival curves for all enrolled patients with impaired and normal RASS can be seen in Figure 3; the survival curve declined more slowly in patients with a normal RASS compared with those with an abnormal RASS.

Using Cox proportional hazards regression, the relationship between an abnormal RASS at initial presentation and 6-month mortality persisted (HR: 1.73, 95% CI: 1.21-2.49) after adjusting for age, sex, nonwhite race, comorbidity burden, severity of illness, dementia, functional dependence, nursing home residence, psychoactive medications given, and admission status. The interaction between an abnormal RASS and APS (severity of illness) had a *P* value of 0.52. The interaction between an abnormal RASS and benzodiazepine or opioid medication administration had a *P* value of 0.38. The interaction between an abnormal RASS and admission status had a *P* value of 0.57. This indicated that severity of illness, psychoactive medication administration, and admission status did not modify the relationship between an abnormal RASS and 6-month mortality.

We analyzed a subset of 406 patients who received a psychiatrist's assessment to determine if an abnormal RASS was associated with 6-month mortality regardless of delirium status using Cox proportional hazard regression weighted by the inverse of the propensity score. Patients with an abnormal RASS and no delirium were significantly associated with higher mortality compared to those with a normal RASS (HR: 2.20, 95% CI: 1.10-4.41). Patients with an abnormal RASS with delirium also had an increased risk for 6-month mortality (HR: 2.86, 95% CI: 1.29-6.34).

All regression models were internally validated. There was no evidence of substantial overfitting or collinearity. The Schoenfeld residuals for each model were examined graphically and there was good model fit overall, and no significant outliers were observed.

TABLE 2. Patient Characteristics

Variables	Normal Arousal, n = 835	Impaired Arousal, n = 249	*P* Value
Median age, y (IQR)	74 (69–80)	75 (70–83)	0.005
Female gender	459 (55.0%)	132 (53.0%)	0.586
Nonwhite race	122 (14.6%)	51 (20.5%)	0.027
Residence			<0.001
Home	752 (90.1%)	204 (81.9%)	
Assisted living	29 (3.5%)	13 (5.2%)	
Rehabilitation	8 (1.0%)	5 (2.0%)	
Nursing home	42 (5.0%)	27 (10.8%)	
Dementia*	175 (21.0%)	119 (47.8%)	<0.001
Dependent†	120 (14.4%)	99 (39.8%)	<0.001
Median Charlson (IQR)‡	2 (1, 4)	3 (2, 5)	<0.001
Median APS (IQR)§	2 (1, 4)	2 (1, 5)	<0.001
Primary complaint			<0.001
Abdominal pain	45 (5.4%)	13 (5.2%)	
Altered mental status	12 (1.4%)	36 (14.5%)	
Chest pain	128 (15.3%)	31 (12.5%)	
Disturbances of sensation	17 (2.0%)	2 (0.8%)	
Dizziness	16 (1.9%)	2 (0.8%)	
Fever	11 (1.3%)	7 (2.8%)	
General illness, malaise	26 (3.1%)	5 (2.0%)	
General weakness	68 (8.1%)	29 (11.7%)	
Nausea/vomiting	29 (3.5%)	4 (1.6%)	
Shortness of breath	85 (10.2%)	21 (8.4%)	
Syncope	46 (5.5%)	10 (4.0%)	
Trauma, multiple organs	19 (2.3%)	8 (3.2%)	
Other	333 (39.9%)	81 (32.5%)	
Benzodiazepines or opioid medications administration	188 (22.5%)	67 (26.9%)	0.152
Admitted to the hospital	478 (57.3%)	191 (76.7%)	0.002
Internal medicine	411 (86.0%)	153 (80.1%)	
Surgery	38 (8.0%)	21 (11.0%)	
Neurology	19 (4.0%)	13 (6.8%)	
Psychiatry	1 (0.2%)	2 (1.1%)	
Unknown/missing	9 (1.9%)	2 (1.1%)	
Death within 6 months	81 (9.7%)	59 (23.7%)	<0.001

NOTE: Patient characteristics and demographics of enrolled patients. Continuous and ordinal variables are expressed in medians and interquartile (IQR) ranges. Categorical variables are expressed in absolute numbers and percentages. *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 >3.38. †Patients with a Katz Activities of Daily Living of <5 were considered to be functionally dependent. There were 19 patients with missing Katz Activities of Daily Living scores. ‡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 score was used quantify severity of illness. Glasgow Coma Scale was not incorporated in this score. Higher scores indicate higher severity of illness.

DISCUSSION

Vital sign measurements are a fundamental component of patient care, and abnormalities can serve as

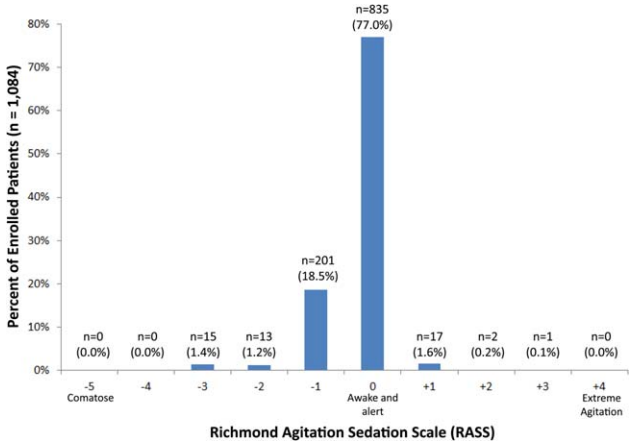

FIG. 2. Richmond Agitation-Sedation Scale (RASS) distribution among enrolled patients. Distribution of RASS at initial presentation among 1084 acutely ill older patients, and of these, 1051 patients (97.0%) were non–intensive care unit patients. The RASS is a widely used arousal scale that can be performed during routine clinical care and takes <10 seconds to perform. A RASS of 0 indicates normal level of arousal (awake and alert), whereas a RASS of <0 indicates decreased arousal and a RASS of >0 indicates increased arousal.

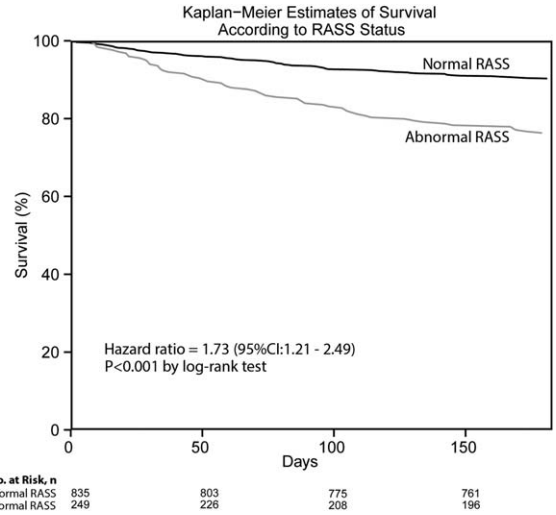

FIG. 3. Kaplan-Meier survival curves in acutely ill older patients with a normal and impaired arousal at initial presentation over a 6-month period. Arousal was assessed for using the Richmond Agitation-Sedation Scale (RASS). Patients with impaired arousal were more likely to die compared to patients with normal arousal (23.7% vs 9.7%) within 6 months. Using Cox proportional hazard regression, patients with an abnormal RASS were 73% more likely to die within 6 months after adjusting for age, dementia, functional dependence, comorbidity burden, severity of illness, hearing impairment, nursing home residence, admission status, and administration of benzodiazepines/opioids medications. Severity of illness ($P = 0.52$), benzodiazepine/opioid medication administration ($P = 0.38$), and admission status ($P = 0.57$) did not modify the relationship between impaired arousal and 6-month mortality. Abbreviations: CI, confidence interval.

an early warning signal of the patient's clinical deterioration. However, traditional vital signs do not include an assessment of the patient's brain function. Our chief finding is that impaired arousal at initial presentation, as determined by the nonphysician research staff, increased the risk of 6-month mortality by 73% after adjusting for confounders in a diverse group of acutely ill older patients. This relationship existed regardless of severity of illness, administration of psychoactive medications, and admission status. Though impaired arousal is closely linked with delirium,[2,24] which is another well-known predictor of mortality,[11,25,26] the prognostic significance of impaired arousal appeared to extend beyond delirium. We observed that the relationship between 6-month mortality and impaired arousal in the absence of delirium was remarkably similar to that observed with impaired arousal with delirium. Arousal can be assessed for by simply observing the patient during routine clinical care and can be performed by nonphysician and physician healthcare providers. Its assessment should be performed and communicated in conjunction with traditional vital sign measurements in the emergency department and inpatient settings.[1]

Most of the data linking impaired arousal to death have been collected in the ICU. Coma, which represents the most severe form of depressed arousal, has been shown to increase the likelihood of death regardless of underlying etiology.[27–31] This includes patients who have impaired arousal because they received sedative medications during mechanical ventilation.[32] Few studies have investigated the effect of impaired arousal in a non-ICU patient population. Zuliani et al. observed that impaired arousal was associated with 30-day mortality, but their study was conducted in 469 older stroke patients, limiting the study's external validity to a more general patient population.[33] Our data advance the current stage of knowledge; we observed a similar relationship between impaired arousal and 6-month mortality in a much broader clinical population who were predominantly not critically ill regardless of delirium status. Additionally, most of our impaired arousal cohort had a RASS of −1, indicating that even subtle abnormalities portended adverse outcomes.

In addition to long-term prognosis, the presence of impaired arousal has immediate clinical implications. Using arousal scales like the RASS can serve as a way for healthcare providers to succinctly communicate the patient's mental status in a standardized manner during transitions of care (eg, emergency physician to inpatient team). Regardless of which clinical setting they are in, older acutely ill patients with an impaired arousal may also require close monitoring, especially if the impairment is acute. Because of its close relationship with delirium, these patients likely have an underlying acute medical illness that precipitated their impaired arousal.

Understanding the true clinical significance of impaired arousal in the absence of delirium requires further study. Because of the fluctuating nature of delirium, it is possible that these patients may have initially been delirious and then became nondelirious during the psychiatrist's evaluation. Conversely, it is also possible that these patients may have eventually

transitioned into delirium at later point in time; the presence of impaired arousal alone may be a precursor to delirium. Last, these patients may have had subsyndromal delirium, which is defined as having 1 or more delirium symptoms without ever meeting full DSM-IV-TR criteria for delirium.[34] Patients with subsyndromal delirium have poorer outcomes, such as prolonged hospitalizations, and higher mortality than patients without delirium symptoms.[34]

Additional studies are also needed to further clarify the impact of impaired arousal on nonmortality outcomes such as functional and cognitive decline. The prognostic significance of serial arousal measurements also requires further study. It is possible that patients whose impaired arousal rapidly resolves after an intervention may have better prognoses than those who have persistent impairment. The measurement of arousal may have additional clinical applications in disease prognosis models. The presence of altered mental status is incorporated in various disease-specific risk scores such as the CURB-65 or Pneumonia Severity Index for pneumonia,[35,36] and the Pulmonary Embolism Severity Index for pulmonary embolism.[37] However, the definition of altered mental status is highly variable; it ranges from subjective impressions that can be unreliable to formal cognitive testing, which can be time consuming. Arousal scales such as the RASS may allow for more feasible, reliable, and standardized assessment of mental status. Future studies should investigate if incorporating the RASS would improve the discrimination of these disease-severity indices.

This study has several notable limitations. We excluded patients with a RASS of −4 and −5, which represented comatose patients. This exclusion, however, likely biased our findings toward the null. We enrolled a convenience sample that may have introduced selection bias. However, our enrolled cohort was similar to all potentially eligible patients who presented to the emergency department during the study period. We also attempted to mitigate this selection bias by using multivariable regression and adjusting for factors that may have confounded the relationship between RASS and 6-month mortality. This study was performed at a single, urban, academic hospital and enrolled patients who were aged 65 years and older. Our findings may not be generalizable to other settings and to those who are under 65 years of age. Because 406 patients received a psychiatric evaluation, this limited the number of covariates that could be incorporated into the multivariable model to evaluate if impaired arousal in the absence of delirium is associated with 6-month mortality. To minimize residual confounding, we used the inverse weighted propensity score, but we acknowledge that this bias may still exist. Larger studies are needed to clarify the relationships between arousal, delirium, and mortality.

CONCLUSION

In conclusion, impaired arousal at initial presentation is an independent predictor for 6-month mortality in a diverse group of acutely ill older patients, and this risk appears to be present even in the absence of delirium. Because of its ease of use and prognostic significance, it may be a useful vital sign for underlying brain dysfunction. Routine standardized assessment and communication of arousal during routine clinical care may be warranted.

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J.H.H., E.W.E., J.F.S., A.B.S., and R.D.S. conceived the trial. J.H.H., E.W.E., A.B.S., J.F.S., R.D.S., A.S., and A.W. participated in the study design. J.H.H. and A.W. recruited patients and collected the data. J.H.H., A.J.G., and A.S. analyzed the data. All authors participated in the interpretation of results. J.H.H. drafted the manuscript, and all authors contributed to the critical review and revision of the manuscript.

The authors report no conflicts of interest.

References

1. Flaherty JH, Shay K, Weir C, et al. The development of a mental status vital sign for use across the spectrum of care. *J Am Med Dir Assoc*. 2009;10:379–380.
2. Chester JG, Beth Harrington M, Rudolph JL, Group VADW. Serial administration of a modified Richmond Agitation and Sedation Scale for delirium screening. *J Hosp Med*. 2012;7:450–453.
3. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. *A new method for detection of delirium. Ann Intern Med*. 1990;113:941–948.
4. 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.
5. 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.
6. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. *J Gen Intern Med*. 1998;13:234–242.
7. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. *Dement Geriatr Cogn Disord*. 2005;19:158–163.
8. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304:443–451.

9. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med*. 2008;168:27–32.
10. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166:1338–1344.
11. 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.
12. 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.
13. 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.
14. 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.
15. Holsinger T, Deveau J, Boustani M, Williams JW Jr. Does this patient have dementia? *JAMA*. 2007;297:2391–2404.
16. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. *Psychol Med*. 1994;24:145–153.
17. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc*. 1983;31:721–727.
18. Murray SB, Bates DW, Ngo L, Ufberg JW, Shapiro NI. Charlson Index is associated with one-year mortality in emergency department patients with suspected infection. *Acad Emerg Med*. 2006;13:530–536.
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818–829.
20. American Psychiatric Association. Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders*: DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Association; 2000.
21. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York, NY: Springer; 2001.
22. Marshall SW. Power for tests of interaction: effect of raising the Type I error rate. *Epidemiol Perspect Innov*. 2007;4:4.
23. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. 2011;46:399–424.
24. Meagher DJ, Maclullich AM, Laurila JV. Defining delirium for the International Classification of Diseases, 11th Revision. *J Psychosom Res*. 2008;65:207–214.
25. McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Arch Intern Med*. 2002;162:457–463.
26. 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.
27. Teres D, Brown RB, Lemeshow S. Predicting mortality of intensive care unit patients. *The importance of coma. Crit Care Med*. 1982;10:86–95.
28. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1:480–484.
29. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F. Predicting outcome from hypoxic-ischemic coma. *JAMA*. 1985;253:1420–1426.
30. Tuhrim S, Dambrosia JM, Price TR, et al. Prediction of intracerebral hemorrhage survival. *Ann Neurol*. 1988;24:258–263.
31. Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA*. 2004;291:870–879.
32. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med*. 2012;186:724–731.
33. Zuliani G, Cherubini A, Ranzini M, Ruggiero C, Atti AR, Fellin R. Risk factors for short-term mortality in older subjects with acute ischemic stroke. *Gerontology*. 2006;52:231–236.
34. Cole M, McCusker J, Dendukuri N, Han L. The prognostic significance of subsyndromal delirium in elderly medical inpatients. *J Am Geriatr Soc*. 2003;51:754–760.
35. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377–382.
36. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.
37. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005;172:1041–1046.