

# Factors Related to the Severity of Delirium in the Elderly Patients With Infection

Gerontology & Geriatric Medicine  
Volume 3: 1–5  
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[sagepub.com/journalsPermissions.nav](http://sagepub.com/journalsPermissions.nav)  
DOI: 10.1177/2333721417739188  
[journals.sagepub.com/home/ggm](http://journals.sagepub.com/home/ggm)



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## Abstract

**Objective:** Delirium is a common neuropsychiatric syndrome in the elderly characterized by concurrent impairments in cognition and behavior. Infection is one of the most important risk factors for delirium. The objective of this study is to elaborate the factors related to the severity of delirium in the elderly patients with infection. **Method:** An observational study on the relationship of several clinical parameters and the severity of delirium in elderly patients (more than 60 years) with infection was conducted at Geriatric Inpatient Ward, Sanglah Hospital. Delirium was defined by the Memorial Delirium Assessment Scale (MDAS). Charlson Age Comorbidity Index (CACI) scores were calculated as proposed by Charlson et al. Infection was confirmed by clinical, laboratory, and radiographic findings. **Results:** During 3 months, there were 60 elderly patients (35 men and 25 women) who were hospitalized with infection and delirium. In all, 33 (55.0%), 16 (26.7%), and 11 (18.3%) patients had pneumonia, urinary tract infection, and other infections, respectively, and 44 out of 60 (73.3%) patients had sepsis. There was no significant difference found in MDAS score between male and female patients and among different types of infection, but patients with sepsis had higher MDAS score significantly compared with patients without sepsis ( $19.48 \pm 3.72$  vs.  $15.88 \pm 2.82$ ;  $p < .001$ ). This study revealed that of several clinical parameters, only CACI ( $R = .533$ ;  $p < .001$ ), blood urea nitrogen (BUN;  $R = .230$ ;  $p = .040$ ), and interleukin 6 (IL-6) levels ( $R = .499$ ;  $p < .001$ ) were correlated with MDAS score significantly. By multiple linear regression test, CACI, IL-6, and sepsis have significant role, meanwhile, BUN has no role, on the severity of delirium. **Conclusions:** The CACI score, IL-6 levels, and sepsis have strong relationship with the severity of delirium, but BUN only has weak role in the severity of delirium in the elderly patients with infection.

## Keywords

infection, delirium, elderly

**Manuscript received:** September 21, 2017; **accepted:** September 25, 2017.

## Introduction

Delirium is an acute syndrome characterized by altered levels of consciousness, attention, and cognitive function (Caplan, 2011). It is a common, life-threatening, and potentially preventable clinical syndrome among elderly persons. The prevalence of delirium at hospital admission ranges from 6% to 56% among general hospital population. Delirium occurs in 15% to 53% of older patients postoperatively and in 70% to 87% of those in intensive care (Inouye, 2006). In the Emergency Department Intermediate Care Unit setting, delirium was associated with longer length of stay and poor outcome at 1 month after discharge, adjusted for age, sex, admission type, presence of systemic inflammatory response syndrome (SIRS) criteria, Charlson score, and osmolality at admission (Mariz et al., 2013). In patients with delirium, the average increase in length of hospital stay is 8 days, and

mortality rates are twice as high compared with similarly matched patients without delirium (McCusker, Cole, Abrahamowicz, Primeau, & Belzile, 2002).

Although it is common, the mechanism of delirium is poorly understood. Risk factors for delirium include dementia, older age, multiple comorbidities, psychoactive medication use, sleep deprivation, dehydration, immobility, pain, sensory impairment, and hospitalization. In frail elderly, delirium may be triggered by many medical and surgical problems, such as metabolic (hyponatremia, hypoglycemia, hypoxemia), infection (urinary

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tract infection [UTI], pneumonia), structural (subarachnoid hemorrhage, urinary retention), toxic (drugs, for example, digoxin, lithium, or poisons), and environmental (being in hospital or emergency department; Caplan, 2011). Over time, a number of theories have been proposed in attempt to explain the process leading to the development of delirium. At least there are top seven theories proposed including neuroinflammatory, neuronal aging, oxidative stress, neurotransmitter deficiency, neuroendocrine, diurnal dysregulation, and network disconnectivity hypotheses (Maldonado, 2013). Infection was the most common cause of delirium in the elderly patients (George, Bleasdale, & Singleton, 1997). It is well known that systemic inflammation can induce a spectrum of changes in central nervous system function through induction of pathogen-associated molecular pattern stimulators of the toll-like receptors or by proinflammatory cytokines. These changes may be described as conserved behavioral and metabolic response to infection, affected to conserve energy and minimize the spread of infection (Cunningham, 2011).

The objective of this study is to elaborate the risk factors related to the severity of delirium among the elderly patients with infections who were admitted at Sanglah Hospital during the 3-month period from January to March 2016.

## Method

An observational study on the relationship of several clinical parameters and the severity of delirium in elderly patients (more than 60 years) with infections at Geriatric Inpatient Ward, Sanglah Hospital, was conducted. All eligible patients were enrolled in the study during the 3-month observation from January until March 2016. The patients were included and evaluated by researchers. If the patients came after office hours, eligible patients were reported to researchers by internal medicine fellows (doctors in specialist training). Patients using antipsychotic drugs, such as anticholinergics, narcotics, benzodiazepines, or hypnotics, were excluded from the study. During the observation period, 60 patients fulfilled the criteria of the study.

All patients were assessed within 24 hr of admission. The existence of delirium was defined by the Memorial Delirium Assessment Scale (MDAS), and suspected infection on admission was defined by clinical findings and confirmed by laboratory examinations and radiographic findings after admission.

In this study, several predicting clinical parameters related to the severity of delirium were measured in the patients, that is, sex, age, Charlson Age Comorbidity Index (CACI), sepsis, blood routine (white blood cells, hemoglobin, platelets), liver function (aspartate transaminase, alanine transaminase, serum albumin), renal function (blood urea nitrogen [BUN], and serum creatinine [SC]), sodium serum (Na), and plasma interleukin 6 (IL-6).

CACI was measured by questionnaire to determine the influence of comorbidities on delirium. The original CACI scores were calculated using the method reported by Charlson, Szatrowski, Peterson, and Gold (1994). The age is adjusted by calculating each decade after 50 years of age. Each decade of age  $\geq 50$  years is equivalent to a 1-point increase in comorbidity (i.e., 50-59 years = 1 point; 60-69 years = 2 points). Type of infection, such as pneumonia, UTI, and other infections, were confirmed by clinical features and supported by laboratory and radiographic examinations. Diagnosis of sepsis was defined by finding of SIRS (requires two or more of the following: temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , heart rate  $>90/\text{min}$ , respiratory rate  $>20/\text{min}$  or  $\text{PaCO}_2 <32 \text{ mmHg}$ , and white blood cells count  $>12,000/\text{mm}^3$  or  $<4,000/\text{mm}^3$  or  $>10\%$  immature band forms) plus confirmed or presumed infections (Inouye, 2006). The MDAS is an instrument commonly used by physician to assess the degree of delirium. The MDAS is a 10-item, 4-point clinician-rated scale (possible range: 0-30) designed to quantify the severity of delirium in medically ill patients. Items included in the MDAS reflect the diagnostic criteria for delirium in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994). A cut-off score of 13 is diagnostic of delirium (Breitbart et al., 1997). Based on MDAS score, delirium can be categorized by three degrees, that is, mild (score: 13-16), moderate (score: 16-24), and severe (score:  $>24$ ) delirium. Plasma IL-6 levels were measured by enzyme-linked immunosorbent assay method with reagent Quantikine.

The characteristics of patients were presented descriptively. Statistical analysis was performed using the software program SPSS Version 23. Independent *t* test and one-way analysis of variance was used to differentiate the levels of MDAS (delirium) among sex, type of infections, and with or without sepsis. One-tailed Pearson correlation test and Spearman  $\rho$  correlation test (only for variable CACI due to abnormal distribution after being analyzed using K-S test) was used to analyze the correlation between several clinical variables and delirium state (MDAS score). Multivariate stepwise linear regression test was used to analyze the role of CACI, sepsis, BUN, and IL-6 (four parameters have relationship with MDAS score) on the severity of delirium. Significant value was confirmed at  $p < .05$ .

The study was approved by Ethical Clearance Committee, Research and Development Unit, Faculty of Medicine, Udayana University/Sanglah Hospital, Denpasar, no: 1490/ UN.14.2/Litbang/2015.

## Results

During 3 months, there were 60 elderly patients who were hospitalized with infection and delirium. In all, 35 (58.3%) patients were men and 25 (41.7%) patients were women; mean of age was  $68.3 \pm 6.58$  (60-83) years. In total, 33 (55.0%) patients had pneumonia, 16 (26.7%) patients had UTI, and 11 (18.3%) patients had

**Table 1.** Characteristic of Patients.

Variables	Frequency or $M \pm SD$ ( $n = 60$ )
Gender: male–female ratio	38 (52.8%): 34 (47.2%)
Aged (year)	$68.03 \pm 6.58$ (60–83)
CACI	$18.52 \pm 3.83$
White blood cells ( $10^9/L$ )	$16.64 \pm 7.65$
Hemoglobin (g/L)	$10.86 \pm 3.30$
Platelets ( $10^9/L$ )	$269.10 \pm 437.70$
Aspartate transaminase (U/L)	$89.53 \pm 129.51$
Alanine transaminase (U/L)	$54.60 \pm 75.18$
Blood ureum nitrogen (mg/dL)	$43.04 \pm 33.06$
Serum creatinine (mg/dL)	$2.57 \pm 2.99$
Fasting blood sugar (mg/dL)	$147.79 \pm 79.47$
Albumin (g/dL)	$2.89 \pm 0.67$
Sodium (mEq/L)	$131.38 \pm 9.49$
Interleukin-6 (pg/mL)	$146.94 \pm 100.79$
MDAS score	$6.13 \pm 1.74$
• Mild delirium	29 (48, 3%)
• Moderate delirium	15 (25%)
• Severe delirium	16 (26.7%)

Note. CACI = Charlson Age Comorbidity Index; MDAS = Memorial Delirium Assessment Scale.

**Table 2.** MDAS Score by Gender, Type of Infection, and Sepsis.

Parameters	MDAS score ( $M \pm SD$ )	$p$
Gender		
• Male	$18.39 \pm 3.76$	.682
• Female	$18.76 \pm 4.00$	
Type of infection		
• Pneumonia	$19.12 \pm 3.89$	.292
• UTI	$17.88 \pm 3.86$	.292
• Others	$17.64 \pm 3.67$	.272
Sepsis		
• Yes	$19.48 \pm 3.72$	<.001
• No	$15.88 \pm 2.82$	

Note. MDAS = Memorial Delirium Assessment Scale; UTI = urinary tract infection.

other infections, and 44 out of 60 (73.3%) patients had sepsis. Based on MDAS score, the frequency of mild, moderate, and severe delirium was 29 (48.3%), 15 (25.0%), and 16 (26.7%) patients, respectively. The characteristics of patients are presented in Table 1.

In this study, there was no significant difference in MDAS score between male and female patients and among different types of infections, but patients with sepsis had higher MDAS score significantly compared with patients without sepsis ( $19.48 \pm 3.72$  vs.  $15.88 \pm 2.82$ ;  $p < .001$ ; Table 2). The study revealed that of several clinical variables, only BUN ( $R = .230$ ;  $p = .040$ ), IL-6 ( $R = .499$ ;  $p < .001$ ), and CACI ( $R = .533$ ;  $p < .001$ ) were correlated with MDAS score significantly (Table 3). By multiple linear regression test, CACI, IL-6, and sepsis have significant role, meanwhile, BUN has no role, on the severity of delirium (Table 4).

**Table 3.** Correlation of Clinical Parameters and MDAS Score.

Parameters	$R$	$p$
Aged (year)	-.103	.218
CACI	.553 <sup>a</sup>	<.001
White blood cells ( $10^9/L$ )	.196	.070
Hemoglobin (g/L)	-.090	.251
Platelets ( $10^9/L$ )	-.179	.090
Aspartate transaminase (U/L)	.063	.326
Alanine transaminase (U/L)	.025	.429
Blood ureum nitrogen (mg/dL)	.230	.040
Serum creatinine (mg/dL)	.116	.191
Fasting blood sugar (mg/dL)	-.169	.098
Albumin (g/dL)	-.155	.118
Sodium (mEq/L)	.042	.375
Interleukin-6 (pg/mL)	.499	<.001

Note. One-tail Pearson correlation test. MDAS = Memorial Delirium Assessment Scale; CACI = Charlson Age Comorbidity Index.

<sup>a</sup>Spearman's rho correlation test.

**Table 4.** The Role of Several Parameters on the Severity of Delirium (MDAS Score).

Model		Unstandardized coefficients		Standardized coefficients		$t$	Significant
		$B$	$SE$	Beta			
1	(Constant)	11.820	1.570			7.529	<.001
	CACI	1.110	0.247	0.512		4.497	<.001
2	(Constant)	11.151	1.447			7.708	<.001
	CACI	0.874	0.235	0.403		3.718	<.001
	IL-6	0.014	0.004	0.380		3.508	.001
3	(Constant)	10.298	1.439			7.158	<.001
	CACI	0.800	0.229	0.369		3.499	.001
	IL-6	0.012	0.004	0.333		3.136	.003
	Sepsis	2.107	0.899	0.243		2.343	.023

Note. MDAS = Memorial Delirium Assessment Scale; CACI = Charlson Age Comorbidity Index.

## Discussion

Based on MDAS score, we found that the frequency of patients with mild delirium was higher than those with moderate and severe ones. Infection is an important risk factor for delirium in the elderly persons. In this study, sex and type of infections were not related to the severity of delirium. However, patients delirium was associated with the presence of SIRS criteria (Mariz et al., 2013). Delirium is also a predictor of in-hospital mortality in elderly patients with community-acquired pneumonia (Pieralli et al., 2014).

Urinary tract infection is related to delirium. A study by Balogun and Philbrick (2014) found that there was relationship between UTI and delirium in the elderly. In subjects with delirium, UTI rates ranged from 25.9% to 32% compared with 13% in those without delirium, and in subjects with UTI, delirium rates ranged from 30% to 35% compared with 7.7% to 8% in those without UTI. Urinary tract infection, but not pneumonia, chronic obstructive airway disease, and acute cardiac syndrome

were related to occurrence of delirium in the acute hospital elderly patients (Collins, Blanchard, Tookman, & Sampson, 2009). This study revealed that the relationship between various types of infection and severity of delirium was not significantly difference.

By bivariate correlation test between clinical parameters and MDAS score, only CACI, BUN, and plasma IL-6 levels have correlation with MDAS score significantly (Table 3). Comorbidity (CACI) is one of the predictors of delirium occurrence among postoperative patients. A study by Korc-Grodzicki et al. (2015) showed that CACI (besides dependence instrumental activities of daily living and fall history) was significantly noted as a predictor of delirium in postoperative elderly patients with cancer. In the acute hospital, laboratory findings were not found to be significantly different in detected and undetected delirium groups in the elderly patients (Collins et al., 2009). Age-adjusted CACI is associated with clinical outcomes or mortality after undergoing cancer surgery. It was associated with treatment decisions and clinical outcomes (Koppie et al., 2008) and postoperative mortality (Haroon, Nadeem, & Ather, 2016) in patients who underwent radical cystectomy in bladder cancer. Multivariate analysis showed that only CACI (odds ratio: 1.8; 95% confidence interval [CI] [1.067, 3.036];  $p = .028$ ) was an independent risk factor of postoperative delirium for the patients more than 70 years of age. The higher CACI score ( $\geq 5$ ) was significantly different from the lower CACI score ( $p < .0001$ ) with respect to postoperative delirium (Ito et al., 2016). Inverse finding was noted by Collins et al., (2009): Patients with undetected delirium was more likely to display high levels of medical comorbidity.

In patients who underwent hematopoietic stem cell transplantation, posttransplantation risk factors for delirium were higher creatinine, higher BUN, lower creatinine clearance, lower oxygen saturation, lower hemoglobin, and lower serum albumin (Weckmann, Gingrich, Mills, & Beglinger, 2012). In acutely admitted elderly patients, cognitive and physical impairment and high serum urea nitrogen concentration were independent risk factors for delirium (Korevaar, van Munster, & de Rooij, 2005). In this study, the severity of delirium was associated with BUN levels, but it was not correlated with SC, hemoglobin, and albumin levels. In this study, reduction in kidney functions is weakly related to the occurrence and severity of delirium.

A proinflammatory state is associated with several age-associated conditions, such as delirium. A study by Liu et al. (2013) in 2013 showed that high serum IL-6 level after surgery was associated significantly with increased risk of the occurrence of postoperative delirium (hazard ratio: 1.514; 95% CI [1.155, 1.985];  $p = .003$ ). A study on the relationship of cytokines and postoperative delirium in older patients who underwent major elective surgery revealed that compared with controls (patients without delirium), cases had significantly higher IL-6 on postoperative day 2 (Vasunilashorn et al.,

2015). The relationship of IL-6 and delirium in the elderly is also noted in studies by Cerejeira, Nogueira, Luís, Vaz-Serra, and Mukaetova-Ladinska (2012) and van Munster et al. (2010). Data from our study confirmed the previous studies, showing that IL-6 is not only a risk factor of delirium but also a valuable predictor of the severity of delirium.

The limitation of this study is that we did not calculate the sample size due to limited study time and instead enrolled all eligible patients during observation period.

## Conclusions

This study showed that infection is an important cause of delirium in elderly patients. In the elderly patients with infection, the CACI score, IL-6 levels, and sepsis have strong relationship with the severity of delirium, whereas BUN only has weak role in the severity of delirium.

## Acknowledgments

The author(s) were grateful to all patients and participants who were involved in this study. This work was supported partly by Sanglah Hospital and Udayana University.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: This paper was written independently. Both authors disclose no financial or personal relationships with other people or organizations that could inappropriately influence the work.

## Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by author and coauthor.

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