

Serum Serotonin Levels and The Severity Scores and Types of Delirium among Geriatric Patients in Denpasar, Indonesia

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ABSTRACT

Introduction: Delirium is an acute attention disorder that often occurs in elderly patients. The serotonergic pathway is the main neurotransmitter pathway involved in the development of delirium. Serotonin, known as 5-hydroxytryptamine (5-HT), affects mood, aggressiveness, cognition, depression, pressure, and stress in the brain environment. This may lead to the formation of hypoactive, hyperactive, or mixed delirium processes. This study utilized laboratory data with the aim of investigating whether serotonin levels have a correlation with severity score and delirium type in elderly individuals who experience delirium during hospitalization.

Methods: This study was conducted in the field of geriatrics at Prof. Dr. IGNG Ngoerah Central General Hospital, Denpasar, Indonesia, from April 2022 to October 2023. The sample was gathered consecutively, consisting of 62 hospitalized geriatric patients who suffered from delirium and were willing to participate by signing an informed consent. We excluded post-surgical patients and psychoactive drug users. The data were collected using the Memorial Delirium Assessment Scale (MDAS), the Confusion Assessment Method (CAM), and a serum serotonin test. This study used bivariate analysis, the Kruskal-Wallis test, and Spearman's correlation ($p < 0.05$).

Results: A total sample of 62 individuals was required. There was a significant difference in the mean serotonin levels among different types of delirium ($p < 0.05$). Out of all the documented cases, hypoactive delirium was the most frequently observed (64.5%). Most of the elderly patients experienced severe delirium (54.8%). Serotonin levels had a significantly negative correlation with the MDAS scores ($r = -0.95$; $p < 0.001$).

Conclusion: The research findings indicate a correlation between lower serotonin levels and higher MDAS scores, and vice versa.

Keywords: Serotonin; Confusion Assessment Method (CAM); Memorial Delirium Assessment Scale (MDAS); geriatrics; human and health

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Highlights:

1. This study attempted to determine the relationship between serum serotonin levels and delirium severity scores among geriatric patients in Indonesia.
2. There was a significant difference in the mean serotonin levels among elderly individuals with hypoactive, hyperactive, and mixed types of delirium.

Article history: •Received 5 February 2024 •Revised 26 March 2024 •Accepted 2 April 2024 •Published 31 August 2024

INTRODUCTION

Delirium is an acute disorder characterized by a decrease in the ability to direct, focus, sustain, and shift attention, as well as a reduced orientation of one's surroundings. It is relatively common among people who are 65 years of age or older. Essentially, delirium reflects the decompensation of brain function as a result of one or more pathophysiological processes. Unfortunately, in many cases, delirium goes undetected or its detection is delayed. A study showed that 32% of patients with delirium were not recognized by doctors, while 40% of delirium cases were misdiagnosed as depression. Patients with delirium exhibit different features

that indicate hyperactive, hypoactive, or mixed delirium (Attard et al., 2008; Steiner, 2011; Schmitt et al., 2019).

Potential mechanisms causing delirium include decreased cerebral blood flow and oxygen extraction by the brain, disruption of the blood-brain barrier, impaired astrocyte function, and neurodegeneration. The development of delirium is associated with the serotonergic pathway, which serves as the main neurotransmitter pathway (Maldonado, 2013; Maldonado, 2018). The serotonergic circuit comprises neurons that produce 5-hydroxytryptamine (5-HT), as well as 5-HT autoreceptors (e.g., 5HT1A, 5HT1B, or 5HT1D

Available at <https://e-journal.unair.ac.id/CIMRJ> ; DOI: 10.20473/cimrj.v5i2.54860



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somatodendritic receptors) and other hormone receptors (e.g., alpha-adrenoceptors, corticotropin-releasing factor receptors, tachykinin receptors, beta estrogen receptors, and oxytocin receptors) (Mulkey et al., 2018). These components play a role in nerve activation and the release of 5-HT.

Studies on the role of serotonin in cognitive disorders are still limited. In light of the limitations of serotonin research, it is important to conduct further studies to mitigate the morbidity, mortality, and distress associated with the care of patients who suffer from delirium. The severity score of delirium can be determined using the Memorial Delirium Assessment Scale (MDAS) method, which allows researchers to conveniently apply it to current studies (Charnay & Leger, 2010; Ploder et al., 2010; van Gool, 2013; Tomasi et al., 2015). In this study, we aimed to conduct an investigation on serum serotonin levels and their correlation with the type and severity score of delirium in geriatric patients.

METHODS

This study analyzed how serum serotonin levels were related to the type and severity score of delirium in geriatric patients. This cross-sectional study observed 62 geriatric patients with delirium at Prof. Dr. IGNG Ngoerah Central General Hospital, Denpasar, Indonesia, in 2022. This study used bivariate analysis, the Kruskal-Wallis test, and Spearman's correlation, with a significance of $p < 0.05$. The data were processed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The samples were selected consecutively from April 2022 to March 2023. The inclusion criteria were geriatric patients who experienced delirium, were being treated at Prof. Dr. IGNG Ngoerah Central General Hospital, and were willing to take part in this research as indicated by informed consent. Patients who underwent surgery and those taking psychoactive drugs were excluded from this study (Pandis, 2014).

We examined the diagnosis of delirium using the Confusion Assessment Method (CAM), the Memorial Delirium Assessment Scale (MDAS) for delirium severity score, and simultaneously measured serotonin levels (Breitbart et al., 1997; Grover, 2012; Growdon et

al., 2022). The types of delirium were divided into three categories: hypoactive, hyperactive, and mixed delirium (Hosker & Ward, 2017; Babacan-Yildiz, 2018). The normal distribution of the sample was assessed using the Kolmogorov-Smirnov test ($p < 0.05$), revealing a non-normal distribution. The Kruskal-Wallis test ($p < 0.05$) was carried out, followed by the Mann-Whitney post-hoc test ($p < 0.05$), to analyze any difference in the serotonin levels among three delirium types (Pandis, 2016). The correlation between serotonin levels and delirium severity scores was analyzed using Spearman's correlation. A multiple linear regression analysis was performed to determine the effect of confounding variables, specifically age and the Charlson Age-Comorbidity Index (CACI) scores, on MDAS scores (Wei et al., 2008; Mercadante et al., 2017; Kirpinar, 2018).

RESULTS

This study examined 62 geriatric patients with delirium who were hospitalized at Prof. Dr. IGNG Ngoerah Central General Hospital, Denpasar, Indonesia. The patients had a median age of 74, with ages ranging from 60 to 92 years old. Out of the 62 subjects, we found that 45.2% were female and 54.8% were male. The serum serotonin levels had a median value of 82.51 ng/mL. The median score for the samples, as measured using the MDAS, was 23. According to the MDAS criteria, the majority of the subjects scored in the severe category, with 34 patients (54.8%). Subsequently, scores that were categorized as moderate were observed in 16 patients (25.8%). The remaining twelve patients (19.4%) yielded scores that fell into the mild category. Table 1 presents the characteristics of the subjects who participated in this study.

The Kolmogorov-Smirnov test revealed that the data on serotonin levels were not normally distributed ($p < 0.001$). This was indicative of the decision to use the non-parametric Kruskal-Wallis test to analyze the three types of delirium, as shown in Table 2.

The Kruskal-Wallis test showed that there was a statistically significant difference in the mean serotonin levels among different types of delirium, as indicated by at least one type group ($H = 33.34$; $p < 0.05$). In order to determine the statistical differences between groups, the Mann-Whitney test was conducted (Figure 1).

Table 1. Characteristics of the research participants who developed delirium

Characteristics	Clinical measurement results (n=62)	
	Median	Mean±SD
Sex		
Male	34 (54.8%)	
Female	28 (45.2%)	
Age (year)	74 (60–92)	74.11±8.55
Systolic blood pressure (mmHg)	110 (80–160)	115.37±19.43
Diastolic blood pressure (mmHg)	70 (50–90)	70.32±9.23
Pulse rate (time/minute)	90 (66–112)	89.32±12.00
Axial temperature (°C)	36.8 (36.0–39.0)	36.9±0.8
CACI score	6.50 (3.00–11.00)	6.85±2.17
MDAS score	23 (8–28)	20.63±5.64
MDAS criteria		
Mild (1–13)	12 (19.4%)	
Moderate (14–22)	16 (25.8%)	
Severe (≥23)	34 (54.8%)	
Serotonin level (ng/mL)	82.51 (32.99–838.62)	148.33±178.92
Delirium types		
Hipoactive	40 (64.5%)	
Hiperactive	13 (21.0%)	
Mixed	9 (14.5%)	

Note: Charlson Age-Comorbidity Index (CACI); Memorial Delirium Assessment Scale (MDAS); standard deviation (SD).

Table 2. Results of the Kruskal-Wallis test between serotonin levels and delirium types

	Delirium types	n	Mean rank	Kruskal-Wallis H	p*
Serotonin levels (ng/mL)	Hipoactive	40	21.90	33.339	<0.001
	Hiperaktif	13	52.77		
	Mixed	9	43.44		

Note: H is the Z-score from the Kruskal-Wallis test; p stands for probability; (*) indicates a significance value of <0.05.

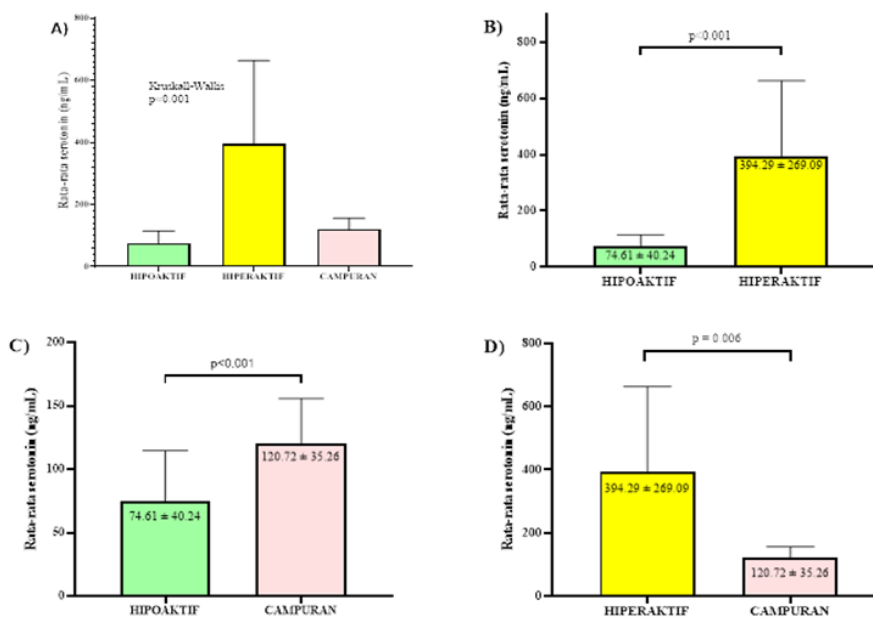


Figure 1. Differences in the average serotonin levels between different types of delirium

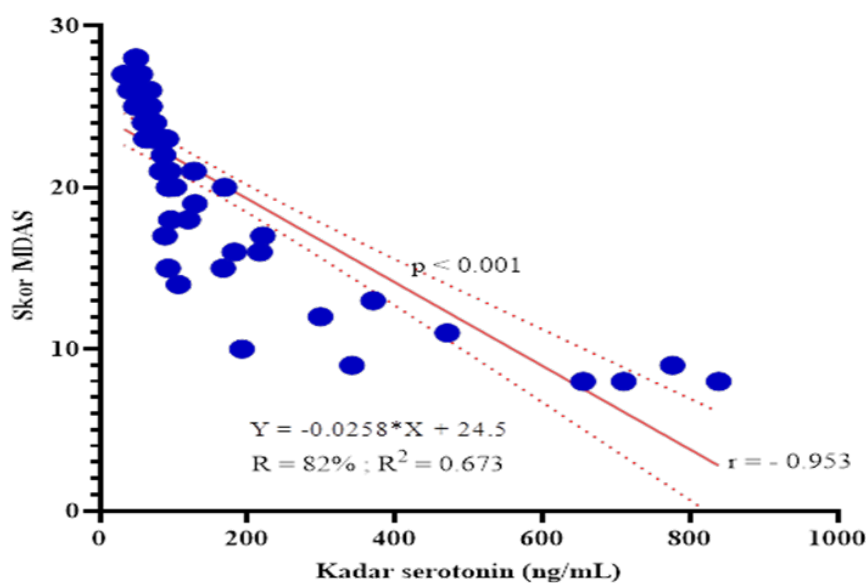


Figure 2. Graph showing the correlation between serotonin levels and MDAS scores

Table 2. Results of the Kruskal-Wallis test between serotonin levels and delirium types

	R (ANOVA)	Unstandardized coefficients		Standardized coefficients	p*	95% CI
		B	SE	Beta		
(Constanta)		17.264	2.651		0.403	
Age (year)	0.924	-0.062	0.034	-0.093	0.073	-0.129–0.006
CACI	(p<0.001)	1.471	0.173	0.567	0.000*	1.124–1.818
Serotonin (ng/mL)		-0.015	0.002	-0.462	0.000*	-0.019–(-0.10)

Note: MDAS scores are the dependent variable; (*) indicates the significant value from the multiple linear regression analysis ($p < 0.05$); Charlson Age-Comorbidity Index (CACI); confidence interval (CI); Memorial Delirium Assessment Scale (MDAS); analysis of variance (ANOVA).

The correlation analysis revealed a significant correlation between the research variables, i.e., serotonin levels and MDAS scores ($p < 0.05$). The correlation coefficient (r value) between the variables was marked as a negative correlation, meaning they moved in opposite directions. The r value was above the range of 0.90, which indicated a very strong correlation. Figure 2 presents the negative correlation ($r = -0.953$; $p < 0.001$), indicating that the higher the serotonin level, the lower the MDAS score.

The multivariate analysis was carried out to determine the contributory relationship between various independent variables and the dependent variable in general. An analysis was performed in this study to examine the impact of the control variables, specifically CACI scores and age, on the MDAS scores as the dependent variable. The results of this analysis are presented in Table 3.

The serotonin level and MDAS score variables showed a very strong correlation, with an inverse variation where the two variables moved in opposite directions ($r = -0.820$; $p < 0.001$). In addition, it was observed that the CACI score variable was significantly correlated with both serotonin levels ($r = -0.644$; $p < 0.001$) and MDAS scores ($r = 0.846$; $p < 0.001$). As the CACI scores increased, the MDAS scores also rose, while the serotonin levels decreased.

The results of the multivariate analysis are presented in Table 3. The R test indicated that the multiple linear regression model incorporating age, CACI scores, and serotonin levels contributed 92.4% of the variance in the MDAS scores ($p = 0.000$).

The F test in analysis of variance (ANOVA) produced a statistically significant value ($p = 0.000$), indicating that the three variables had a simultaneous impact on the MDAS scores. The data demonstrated that serotonin levels remained unaffected by other control variables that were tested for correlation at this advanced stage ($p < 0.001$). The relationship of multiple linear regression was expressed by the equation $y = -0.015X_1 + 1.471X_2 + 17.3$, where the MDAS scores decreased by 0.015 times. For every one-unit increase in the CACI scores, the MDAS scores increased 1.47 times.

DISCUSSION

The current research involved research participants who were classified as elderly, with an average age of over 60 years. Prior research by Ahmed et al. (2014) emphasized age as the most frequently recorded risk factor in delirium patients. Older age was significantly associated with an increased risk of delirium, according to the pooled analysis (95% CI=0.11–5.38, $p = 0.04$). Likewise, Kim et al. (2016) asserted that age and gender, which cannot be changed through medical intervention, are the main demographic risk factors for delirium. Even though the percentage of male patients was greater in this study, the resulting logistic

regression value did not reach statistical significance. In this sense, gender did not have much influence on the incidence of delirium experienced by the research participants. These results are similar to the findings of a study conducted by Kuswardhani & Sugi (2017). Their study found that there were no significant differences in MDAS scores between male and female patients ($p = 0.682$).

This study found significant differences in the average serotonin levels among different groups of delirium types. The results of the current study are in line with other previous studies that showed a higher prevalence of hypoactive delirium compared to hyperactive delirium in patients over 65 years of age (Boettger & Breitbart, 2011; Hayhurst et al., 2020). The current research revealed that patients with hypoactive delirium exhibited more severe degrees of delirium. In this regard, routine assessment of delirium in the intensive care unit (ICU) is of the utmost importance. Without routine screening, most cases of hypoactive delirium are left undiagnosed, which may lead to unfavorable outcomes (Hayhurst et al., 2020).

The results of a study conducted by Lawlor et al. (2020) support the current research, which found that the severity of delirium influenced the condition of geriatric patients. According to the results of the correlation analysis, serotonin levels and MDAS scores were correlated with each other, with a significance value of $p < 0.05$. The correlation coefficient (r value) between the variables demonstrated a negative correlation. This result indicated that serotonin levels and MDAS scores moved in opposite directions. As serotonin levels increased, MDAS scores decreased. Serotonergic deficits can manifest in several ways, including reduced availability of precursors, impaired tryptophan hydroxylase activity, abnormalities in 5-HT release or uptake, abnormalities in 5-HT receptors, or interactions with other neurotransmitters (Lawlor et al., 2020).

In the multivariate analysis, it was shown that serotonin levels and MDAS scores still showed a very strong correlation, with a negative variation ($r = -0.820$; $p < 0.001$). The results of the multivariate analysis revealed that only CACI scores were identified as an independent risk factor for postoperative delirium in patients aged older than 70 years. Prior research by Kuswardhani & Sugi (2017) demonstrated that in elderly patients who experienced infections, the CACI scores and sepsis had a strong relationship with the degree of delirium, while blood urea nitrogen only had a weak role in the degree of delirium. Similarly, in a prior study conducted by Ito et al. (2017), they assessed CACI scores (OR 1.8; 95% CI 1.067–3.036; $p = 0.028$) and discovered that higher CACI scores were deemed a significant risk factor for delirium in patients older than 70 years.

This study has an advantage from the new data obtained on the inverse relationship between serum serotonin levels and delirium severity scores. The findings of this study offer

additional evidence that there was a significant difference in the mean serotonin levels across individuals with different delirium types. However, a limitation of this study was that it did not examine in depth the role of serotonin, which cannot be separated from other neurohormonal links.

CONCLUSION

Mean serotonin levels significantly varied among different types of delirium, which include hypoactive, hyperactive, and mixed delirium. Additionally, there was also an inverse correlation between serotonin levels and the severity scores of delirium.

ACKNOWLEDGEMENT

The authors would like to thank Prof. Dr. IGNG Ngoerah Central General Hospital, Denpasar, Indonesia, for providing support in conducting this study.

CONFLICT OF INTEREST

This study was free from any conflict of interest.

ETHICS CONSIDERATION

This study obtained ethical approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Udayana, Denpasar, with registration No. 2800/UN14.2.2.VII/LT/2022 on October 27, 2022.

FUNDING DISCLOSURE

The authors did not receive funding from any parties.

AUTHOR CONTRIBUTION

IMDK contributed to the conception and design, analysis and interpretation of the data, final approval of the article, provision of administrative, technical, or logistic support, and collection and assembly of the data. NA drafted the article and provided funding. LSK was responsible for gathering study materials or patients. IGPSA contributed to the critical revision of the article for important intellectual content and statistical expertise.

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