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Low plasma levels of IGF-1 and IL-1RA with high plasma levels of IFN- γ as prognostic factor for mortality in hospitalized geriatric patients with delirium



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ABSTRACT

Background: Delirium is common and serious problem with high morbidity and mortality, especially in geriatric patients. Decrease in the number of neuroprotective factors (IGF-I and IL-1RA) and increase in IFN- γ had been correlated with the incidence of delirium. This study aims to understand whether these markers can be used as predictors for mortality in geriatric patients with delirium in an effort to prevent the adverse events of delirium.

Methods: In this observational analytic study with prospective cohort design carried out in the Geriatric Installation care room at Sanglah General Hospital in Denpasar in 2018, 76 samples were examined for their IGF-1, IL-1RA, IFN- γ plasma levels. Patients were then followed during their hospital stay until they were declared cured or died due to delirium or its complications. The relationship

between each group and mortality rate were then analyzed using univariate, bivariate and multivariate analysis.

Results: In this study, median was used as the cutoff point for IGF-1 levels [21.38 (0.00-91.07)], IL-1RA levels [2,491.48 (193,44-6720,13)] and IFN- γ [194.29 (0.00-2200.96)]. In multivariate analysis, low plasma levels of IGF-1 (HR= 4.12 [95% CI: 1,458 - 11,642, p=0.008]) and IL-1RA (HR=2.91 [95 % CI: 1.037 - 8.154, p= 0.043]) proved to be an independent factor in the occurrence of death in geriatric patients with delirium. However, IFN- γ failed to show any correlations.

Conclusion: Both low plasma levels of IGF-1 and IL-1RA can be used as predictors for mortality in geriatric patients with delirium.

Keywords: delirium, geriatric, IGF-1, IL-1RA, IFN- γ

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INTRODUCTION

Nowadays, there has been an increase in life expectancy due to developments and advancements in the field of medicine resulting in an increase in elderly population. Delirium is common and serious problem with high morbidity and mortality, especially in geriatric patients. Delirium results in increased length of stay, complications, and increased mortality by up to 76%.^{1,2}

The pathophysiology of delirium is multifactorial and involves dynamic interactions of various risk factors. One theory that can explain the pathophysiology of delirium is the theory of neuro-inflammation.³ Several studies have shown that low levels of both neuroprotective factors (IGF-I, IL-1RA) and increase in IFN- γ circulating levels are significantly associated with the severity of delirium. IFN- γ secretion in the brain can cause declining cognitive function and neurobehavioral symptoms such as anxiety, depression and psychosis.^{4,5} However, there are also some contradictory studies

regarding the findings above. In addition, no studies have used plasma IGF-1, IL-1RA, IFN- γ levels as prognostic factors in predicting mortality in delirium patients.⁶ Therefore, the purpose of this study was to determine the relationship of IGF-1, IL-1RA and IFN- γ as prognostic factors in the incidence of death in hospitalized geriatric patients with delirium in an effort to prevent adverse events of delirium.

METHODS

Ethical approval for this study (44/UN.14.2/KEP/2018) was provided by the Ethical Committee of Udayana University/Sanglah General Hospital, Bali. This study is an observational analytic study with prospective cohort design. The study was conducted in the care room of the Geriatric Installation in Sanglah General Hospital, Denpasar, in one-year period with sample size of 76 samples. The inclusion criteria in this study was all geriatric patients with delirium treated in the care room of

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Geriatric Installation in Sanglah General Hospital with standard treatment for delirium and its complications. While the exclusion criteria were patients with immune system abnormalities, malignancy and history of corticosteroid use for at least the past two weeks. Patients who met these criteria were then taken as much as 5ml of venous blood samples for examination of IGF-1, IL-1RA, and IFN- γ levels using the ELISA method. In addition, comorbid index was also measured with the Cumulative Illness Rating Scale (CIRS). The severity of delirium was measured using the Memorial Delirium Assessment Scale (MDAS) questionnaire. And the dependence index was measured with Barthel's Activities of Daily Living (ADL) score.

Patients were then grouped into several categories based on their IGF-1, IL-1RA and IFN- γ levels with median as cut-off point. These categories include patients with low and normal plasma IGF-1 levels, patients with low and normal plasma IL-1RA levels and patients with high and normal IFN-plasma plasma levels. During their hospital stay, patients were then followed until they

were declared cured or died from delirium and its complications. For the characteristics of samples, descriptive analysis was carried out. To assess the relationship between independent variables and mortality rate, Chi-square test was used. The Kaplan-Meier survival curve with log rank test was used to analyze the relationship between risk factors (low plasma IGF-1 levels, low plasma IL-1RA levels and high IFN-plasma plasma levels) and mortality. Cox proportional test was carried out to assess the Hazard Ratio (HR) between low plasma IGF-1 levels, low plasma IL-1RA levels, high plasma IFN- γ levels and mortality rate by controlling confounding variables. The level of significance (α) used in this study was probability value (p) of less than 0.05.

RESULTS

The sample characteristics are presented in [Table 1](#). Based on the results of descriptive statistics, the range of IGF-1 levels is 0.00-91.07 (mean: 26.62; median: 21.38; standard intersection: 20.85), the range of IL-1RA levels is 193.44- 6720.13 (mean: 2574.66; median: 2491.48; standard intersection: 1324.2), and the range of IFN- γ levels is 0.00-2200.96 (mean: 386.33; median: 194.29; standard intersection: 480.82). There was a significant difference between patients with low serum IGF-1 levels and patients with normal serum IGF-1 levels ($p=0.03$). The survival rate of patients with low serum IGF-1 levels was $34.97 \pm 6, 09$ days (95% CI = 23,022 - 46,930), whereas the survival rate of patients with normal serum IGF-1 levels was 38.38 ± 5.21 days (95% CI = 28,187 - 48,590). In addition, it was found that the survival rate between patients with low serum IL-1RA levels and normal serum IL-1RA levels differed significantly ($p=0.01$). The survival rate of patients with low serum IL-1RA levels was 31.94 ± 6.55 days (95% CI = 19.102 - 44,779), whereas the survival rate of patients with normal serum IL-1RA levels was 40.33 ± 3.87 days (95% CI = 32,750 - 47,916). However, the survival rate between patients with high serum IFN- γ values and normal IFN- γ serum values was different but not significant ($p=0.435$).

In multivariate analysis using Cox Proportional Hazard regression analysis, low serum IGF-1 levels and low serum IL-1RA levels were found to be an independent factor in the occurrence of death in geriatric patients with delirium. The hazard ratio for both low serum IGF-1 levels and low serum IL-1RA levels were 4,12 (95% CI: 1,458 - 11,642, $p=0.008$) and 2,91 [95 % CI: 1.037 - 8.154, $p= 0.043$], respectively. However, the value of serum IFN- γ levels was not proven to be an independent factor in the occurrence of death in patients with delirium.

Table 1. Sample Characteristics

	Mean \pm SD or median (minimum-maximal values) or frequency	
	Live (n=51)	Death (n=25)
Age (years)	73,3 \pm 7,5	72,6 \pm 8,3
Gender (%)		
Male	21 (41,2%)	14 (56,0%)
Female	30 (58,8%)	11 (44,0%)
CIRS* comorbid score	11,3 \pm 5,4	14,8 \pm 7,0
MDAS† score	18 (2-30)	25 (10-30)
Mild	21 (41,2%)	5 (20,0%)
Moderate	21 (41,2%)	14 (56,0%)
Severe	9 (17,6%)	6 (24,0%)
ADL** score	5 (0-18)	2 (0-16)
Total dependency	22 (43,1%)	22 (88,0%)
Severe dependency	13 (25,5%)	0 (0,0%)
Moderate dependency	10 (19,6%)	0 (0,0%)
Mild dependency	6 (11,8%)	3 (12,0%)

*Cumulative Illness Rating Scale

†MDAS : Memorial Delirium Assessment Scale

**ADL : Activity Daily Living

Table 2 Cox Proportional Hazard Analysis between serum levels of IGF-1, IL-1RA, IFN- γ and mortality rate

Variables	p value	HR	95% CI
IGF-1	0,008	4,12	1,458 – 11,642
IL-1RA	0,043	2,91	1,037 – 8,154
IFN- γ	0,509	1,34	0,560 – 3,217

Therefore, it cannot be used as a prognostic factor in the incidence of death in geriatric patients with delirium.

DISCUSSION

Many prognostic factors are known to be associated with death in geriatric patients with delirium, ranging from physical disability, disease severity, comorbidities, and functional status.^{7,8} Researches on identifying prognostic factors of delirium have been carried out with varying results. Previous studies showed that delirium patients with severe comorbid and male sex have higher mortality rate. Delirium episodes are also last longer in patients with dementia rather than in patients without dementia.²

Studies showed that low plasma IGF-1 levels and low plasma IL-1RA levels can be used as the prognostic factors of mortality in geriatric patients with delirium. The results of this study are similar with the research conducted by Adamis et al. in 2009 which showed that low levels of both neuroprotective factors (IGF-I, IL-1RA) were significantly correlated with the severity of delirium ($p < 0.05$).⁴

In this study, high serum IFN- γ levels were not associated with higher mortality rate in geriatric patients with delirium. This result is not in accordance with the results of a study conducted by Adamis et al in 2009 which found that high serum IFN- γ levels affected the incidence of death in delirium patients (HR 1.24; $p < 0.05$). However, the results of this study is similar with a study conducted by Ripper et al. 2016 which found that there were also no significant differences in IFN- γ levels in patients who died compared to those who were still alive in hospitalized delirium patients ($p > 0.05$).⁹ Given the fact that there is variability in fluctuating cytokine levels, it is necessary to examine IFN- γ biomarker levels for at least twice.

Low IGF-I levels has been associated with the incidence of delirium. IGF-I has a major role in terms of building and maintaining neuron survival, also in proliferation, differentiation and synaptogenesis. It is interesting to mention that neurons are directly

protected by IGF-I, and not through other indirect mechanisms that involve IGF-I stimulation or additional trophic support from glia. It is also important to mention that IGF-I is an anabolic hormone mainly synthesized in the liver under the control of pituitary growth hormone (GH). During aging, there is gradual decline and alteration in GH secretion pattern and IGF-1 production. This phenomenon, so called "somatopause", contributes to a characteristic relative anabolic hormone deficiency in the elderly which directly correlates with health status and frailty.¹⁰ IGF-I also has cognitive reserve ability. IGF-I, through modulation of membrane channels and neurotransmission, impinges directly on neuronal plasticity, the cellular substrate of cognition.¹¹

IL-1RA inhibits the action of IL-1 α and IL-1 β , both of which are pro-inflammatory cytokines which have a direct or destructive effect on other pathways in the brain. IL-1RA prevents ischemia, prevents nerve damage and inhibits the induction of inflammatory reactions by β -amyloid peptides.^{4,5}

On the other hand, IFN- γ has several effects on the brain including inducing neuronal development, downregulating glutamate receptors and increasing neuronal activity in the hippocampus. The secretion of IFN- γ in the brain can also cause cognitive function degradation. IFN- γ also plays an important role in various neurobehavioral symptoms such as anxiety, depression, psychosis, sleep and arousal which are all common symptoms of delirium.⁶

This study illustrates that poor predisposing factors play a greater role as prognostic factors of death in delirium patients compare to any precipitating factors.

CONCLUSION

Both low plasma levels of IGF-1 and IL-1RA can be used as predictors in mortality in geriatric patients with delirium. However, high plasma levels of IFN- γ failed to show any correlation with mortality rate in hospitalized geriatric patients with delirium.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL CLEARANCE

Ethical approval for this study (44/UN.14.2/KEP/2018) was provided by the Ethical Committee of Udayana University/Sanglah General Hospital, Bali.

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AUTHOR CONTRIBUTION

All authors are equally contributed to the study from manuscript preparation, data analysis, until reporting the results of study.

CONFLICT OF INTEREST

The authors declare that do not have any financial relationship. The authors declare that they have no conflict of interest.

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