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# High interleukin-6 level increases depression risk on geriatric population in Denpasar, Bali-Indonesia



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## ABSTRACT

**Background:** High interleukin-6 (IL-6) serum level was responsible in inflammatory regulation through the interaction within macrophage, glial melatonin production and regulation of *methyl CpG-binding protein 2* (MeCP2) and influenced neuro-inflammation process, thus, it increased the risk of depression. The aim of this study was to determine whether high interleukin-6 serum level increased the risk of depression in geriatrics.

**Methods:** A case control was performed as the design of this study. Geriatric populations with depression enrolled as the case group and without depression as control group. Assessment of IL-6 serum level was conducted by the patient's venous blood. The IL-6 serum > 10 pg/ml was categorized as high.

**Results:** In this study, 30 cases and 30 controls who met the criteria included as samples. There were 20 males (66.7%) and 10 females (33.3%). Factors associated with an increased risk of depression in geriatric were a high level of serum interleukin-6 (OR=3.60; CI95%: 1.22-10.64, p=0.018) and a marital status (OR=3.50; CI95%: 1.11-11.02, p=0.028). High level of interleukin-6 was a significant and an independent risk factor of depression in geriatric (OR=3.60; CI95%: 1.22-10.64, p=0.021) in multivariate analysis.

**Conclusion:** This study concluded that high IL-6 serum level increased the risk of depression in geriatric.

**Keywords:** serum interleukin-6 level, risk, depression in geriatric

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## INTRODUCTION

Geriatric populations increased in the 21<sup>st</sup> Century, including in Indonesia. It reflected the demographic transition when the geriatric populations kept growing whilst younger population proportion was steady or even less. Men's life expectancy has kept growing over times with a multifactorial cause. In Indonesia, life expectancy had been increasing from year 1970 until year 2000. Female's life expectancy was 48.1 to be 70 years, while male's was lower, which was 45 to be 65 years. Based on Indonesian Statistics Central data on 1990-2025 in year 2015, geriatrics were 7.28% ( $\pm$  15.2 millions) from total Indonesian populations. It was estimated that geriatrics would be 11.34% of world populations by 2020.<sup>1</sup>

Epidemiology pattern would be changed by demographic changes including lifestyle and eating habits. Non-infection diseases were the causes of 40% death cases in developing countries, one of which was depression.<sup>2</sup> Depression was one of mental disorders which often found on geriatric patients. Depression generally marked by sadness, loss of excitement over activities, weakness, fatigue, and feeling of helplessness. In geriatric patients, the main symptoms were somatic pain, loss of appetite and sleeping disturbance.<sup>3</sup>

Our knowledge of depression had been changing. In the last 2 decades, experts often debated whether

depression were related to inflammation process. Inflammation was expected to be a process that change the brain structures and functions. Bryant *et al.* (2009) stated that IL-6 was one of inflammatory factors that influence depression.<sup>4</sup> Some studies had proven that IL-6 was an inflammatory mediator that predisposed to depression, and in the other hand, some studies had failed to prove the correlation between depression and inflammatory process. A study by Li *et al.* (2007) and Gao *et al.* (2009) failed to prove that correlation.<sup>5,6</sup>

As what had been known, geriatrics often encountered with the increase of pro-inflammatory cytokine, one of which was IL-6. High IL-6 serum level in geriatrics had been thought to have important role, so that geriatrics tended to get depression easier compared to adults.<sup>7</sup>

The purpose of this study was to analyze whether high interleukin-6 serum level would increase the risk of depression in geriatric.

## MATERIALS AND METHODS

A case control was performed as the design of this study in geriatric populations (over 60 years) at eight banjar (i.e. similar to district) in Denpasar which were Tegal Dukuh Anyar, Penamparan, Sedana Merta, Kerta Bhuwana, Lebah, Dalem, Lantang

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Bejuh and Panti. Sixty patients were enrolled in the study. Patients with acute or chronic infection, acute or severe inflammation and those having an autoimmune disease, those having psychiatric disorders, consuming aspirin, NSAID, corticosteroids, barbiturates group, opioid, codein, morfin in the last 2 weeks, and patient with depression that had already receiving treatments were excluded from the samples.

Several variables were measured from samples including age, sex, status marital status, monthly incomes, and IL-6 serum level. Depression was measured by 2 psychiatric *chief* residents at Udayana Medical Faculty/Sanglah Hospital using DSM IV. Subjects were divided into 2 groups, those with depression as case group dan without depression as control group.

Assessment of IL-6 serum level was conducted at *Prodia* Laboratory in Denpasar using subjects' venous blood with *Human Interleukin 6 Immunoassay (Quantikine)* as an assessment method and was stated in pg/mL.

Data was analyzed using two statistic steps, a descriptive statistic to observe the subjects' characteristics and analytical to determine the odds ratio (OR) and 95% Confidence Interval (95% CI). Hypothesis testing using bivariate analysis with Chi-Square method for nominal scale on both independent and dependent variables. Multivariate analysis was used to control the confounding variables using logistic regression for nominal scale on both independent and dependent variables<sup>8</sup> and was classified as significant if  $p$  value < 0.05. This study was approved by Ethical Clearance Committee, Research and Development Unit, Faculty of Medicine Udayana University/Sanglah Hospital, Denpasar, No: 1495/UN.14.2/Litbang/2014.

## RESULTS

During the study period (December 2014-June 2015), there were 40 depression subjects living in Denpasar. Ten from which were excluded for various reasons. Four subjects were excluded for consuming NSAID in the last 2 weeks, 3 for consuming anti-depression drugs, and 3 for having an acute infection. The rest 30 depression subjects were categorized as cases and 30 non-depressed subjects as control. Subjects' characteristics as seen on [Table 1](#).

The mean age of all subjects was  $66.03 \pm 5.44$  year, with mean age on case group was  $67.50 \pm 1.25$  year and control group was  $64.57 \pm 0.54$  year, indicating that case group had an older mean age compared to control group.

IL-6 serum level was divided into 2 categories which were high IL-6 serum and normal IL-6

serum. It was categorized as high if the level > 10 pg/ml and normal if the level  $\leq 10$  pg/ml.<sup>9</sup> Bivariate analysis showed the correlation between age, sex, income, marital status and IL-6 serum level variables with depression on geriatrics. [Table 2](#) served the bivariate analysis.

In case group, high IL-6 serum level was found on 17(56.7%) subjects and normal level on 13(43.3%). In control group, high IL-6 serum level was obtained on 8(26.7%) and normal level on 22(73.3%). High IL-6 serum level was significantly related to the increasing risk of depression on geriatrics with OR=3.60; 95% CI: 1.22-10.64,  $p$  value=0.018, which meant that subjects with high IL-6 serum level had 3.6 times higher risk on getting depression compared to subjects with normal IL-6 serum level.

Marital status was significantly correlated to the higher risk of depression on geriatrics (OR=3.50; 95% CI: 1,11-11,02,  $p=0,028$ ), which meant widower geriatric had 3.5 higher risk on getting depression.

Age, sex, and monthly income didn't significantly correlate with the risk of depression on geriatrics. Variables with  $p$  value < 0,25 on bivariate analysis would be re-analyzed using multivariate analysis. Multivariate analysis was conducted to obtain the independent risk factors on geriatrics depression ([Table 3](#)).

In this study, only IL-6 serum level was statistically significant as an independent risk factors of

**Table 1** Subjects Characteristics

Variables	Case n=30	Control n=30
<b>Age (year), mean<math>\pm</math>SD</b>	67,50 $\pm$ 1,25	64,57 $\pm$ 0,54
> 66	14(46,7%)	9(30,0%)
$\leq$ 66	16(53,3%)	21(70,0%)
<b>Sex</b>		
Male	20(66,7%)	17 (56,7%)
Female	10(33,3%)	13(43,3%)
<b>Marital Status</b>		
Married	16(53,3%)	25(83,3%)
Widower	14 (46,6%)	5(16,6%)
<b>Occupation</b>		
Civil Servant	0(0%)	1(3,3%)
Self-employed	15(50,0%)	9(30,0%)
Pensioner	8(26,7%)	17(56,7%)
Unemployed	7(23,3%)	3(10,0%)
<b>Ethnicity</b>		
Balinese	27(90,0%)	25(83,3%)
Non-Balinese	3(10,0%)	5(16,7%)
<b>Income</b>		
< 2 million	22(73,3%)	19(63,3%)
$\geq$ 2 million	8(26,7%)	11(36,7%)
<b>IL-6 serum level (pg/ml) <math>\pm</math>SD</b>	11,17 $\pm$ 2,32	5,13 $\pm$ 3.70

**Table 2** Bivariate analysis on age, sex, income, marital status and IL-6 with depression on geriatrics

Variables		Case n (%)	Control n (%)	OR	P value (95% CI)
Age	>66 years	14(46,7%)	9(30,0%)	2,04	0,184 (0,71-5,90)
	≤66 years	16(53,3%)	21(70,0%)		
Sex	Male	20(66,7%)	17(56,7%)	1,53	0,43 (0,54-4,36)
	Female	10(33,3%)	13(43,3%)		
Income	<2 millions	22(73,3%)	19(63,3%)	1,59	0,41(0,53-4,78)
	≥2 millions	8(26,7%)	11(36,7%)		
Marital status	Widower	14(46,6%)	5(16,6%)	3,50	0,028*(1,11-11,02)
	Married	16(53,3%)	25(83,3%)		
IL-6 serum level (pg/ml)	High (>10,0)	17(56,7%)	8(26,7%)	3,60	0,018*(1,22-10,64)
	Normal (≤10,0)	13(43,3%)	22(73,3%)		

\*p value&lt;0,05

**Table 3** Multivariate analysis of risk factors on geriatric depression

Variable	Coefficient	OR	P value (95% CI)
Age	0,02	1,02	0,98 (0,28-3,69)
Marital	0,89	2,43	0,16 (0,70-8,36)
IL-6 serum level	1,28	3,60	0,021* (1,22-10,64)

\*p value&lt;0,05

depression on geriatrics (OR=3,60; 95% CI:1,22-10,64, p=0,021). Subjects with high IL-6 serum level had 3,6 times higher risk on getting depression compared to normal or even low IL-6 serum level, whereas other factors such as age and marital status were not statistically significant as independent risk factors.

## DISCUSSION

Depression was a disorders which generally marked by sadness, guilty feelings, community withdrawal, sleeping disturbance, loss of appetite, sexual, and loss of enjoyment from daily activity. Depression often related to other psychology problems such as panic attack, drug abuse, sexual dysfunction and personality disorders.<sup>10</sup> Depression on geriatrics often manifested as mild to severe depression, marked by many depression symptoms. Several studies concluded that depression was one of the most frequent causes of emotional disturbance, resulting in the decreasing of geriatrics' quality of life.<sup>11</sup>

Age was correlated to depression, which might be caused by the reduction of brain cell defense mechanism as men aged, resulting in geriatrics tended to encounter depression easier. Depression might be a chronic disorder if it first appeared at age above 60 years. Based on a study on geriatrics

with depression followed for 6 years, 80% of whom didn't resolve and continued having depression or having tidal phase of depression.<sup>12</sup> This study was a little different from Western studies, where depression was found mostly on age <66 year (53,3%) compared to age > 66 year (46,7%), which might be caused by Indonesian culture. In Indonesia, elders were highly honored, thus might be a factor that prevent depression on geriatrics.

This study found that subjects with depression was predominantly males compared to females with 20(66,7%) were males and 10(33,3%) were females. Based on age, this study result was different compared to study conducted by Wijeratne *et al.* (2000) in which found that males (46.4%) were more than females (53.6%) in geriatrics with depression. A study by Cesar *et al.* (2013) in Brazil also had a parallel result with depression subjects were predominantly females compared to males (63% vs 37%).<sup>13</sup> There were also a study that found males was more predisposed to depression compared to females. Sidik *et al.* (2003) obtained that male geriatrics had more depression disorders compared to females (56% vs 43%).<sup>14</sup>

Definite reasons why depression on geriatrics were consistently found more on females had not been known. Hormonal factors were thought to be the influences. Estrogen and progesterone had been showed influencing neurotransmitter, neuroendocrine and circadian system which involved in mood disorders.<sup>15</sup>

This study, based on marital status, found a parallel results compared to other studies. A study conducted by Sherina *et al.* (2004) found that geriatrics with depression were predominantly widowers compared to those living with their spouse.<sup>16</sup>

In this study, subjects in case group with income less than 2 million rupiah had a bigger proportion, which were 22(73,3%), whereas those in control groups with income less than 2 million

rupiahs were 19(63,3%). Socio-economic problems remained one of risk factors of geriatric depression. This was parallel to a study by Sherina *et al.* (2004) which found that geriatrics with low socio-economic class had a bigger proportions compared to those with high socio-economic status (58,2% vs 41,8%) respectively.<sup>16</sup> Nevid *et al.* (2004) stated that those with lower socio-economic class had a higher risk on getting depression, which might be caused by many factors such as inadequate nutrition, poor sanitation, poor health status, and combinations of unorganized family and community life.<sup>17</sup>

Mean IL-6 serum level was higher at subjects with depression compared to control. Mean IL-6 serum level in depression group were  $11,17 \pm 2,32$  pg/ml, whereas in control group were  $5,13 \pm 3,70$  pg/ml. This result was parallel with a study conducted by Uglesic *et al.* (2015) which obtained mean IL-6 serum level in depression subjects was  $4,26 \pm 2,83$  pg/ml, which was higher compared to non-depression subjects with mean serum level  $0,92 \pm 0,99$  pg/ml, but, instead of geriatric population, this study was conducted on dialyzed patients.<sup>18</sup> Increase of IL-6 serum level and other cytokines such as IL-1 and TNF- $\alpha$  on depression were frequently found as with other psychiatric disorders. Rise of IL-6 on depression were expected to be correlated with the increase of hypothalamus-pituitary-adrenal (HPA) axis, increasing cortisol, which changed tryptophan 2,3-dioxygenase (TDO) activity and would decrease the tryptophan availability with serotonin, resulting in stress and depression. Therefore, IL-6 played an important role on biological pathway that underlying stress and depression which precipitated by stress.<sup>19</sup>

In this study, high IL-6 serum level was significantly related to higher risk of depression on geriatrics (OR=3,60; 95% CI: 1,22-10,64, p value=0,018). This result was parallel with other studies, but the samples were not geriatrics. In a study conducted by Lu *et al.* (2013), mean IL-6 serum level on depression subjects with COPD was  $7,39 \pm 1,21$  pg/ml, higher than control group which was  $3,19 \pm 1,41$  pg/ml. IL-6 serum level on case group was significantly higher compared to control ( $p \leq 0,001$ ).<sup>20</sup> Meyer *et al.* (2011) obtained the same result, in which IL-6 induced depression, but this study's population was cardiovascular patients.<sup>21</sup>

Overall, IL-6 had an important role in inducing depression on geriatrics. Increase of IL-6 was related to inflammation regulation though the interaction with macrophage and glia melatonin production and methyl CpG-binding protein 2 (MeCP2) regulation, resulting in the decrease of serotonin, melatonin and N-Acetyl Serotonin (NAS) production which had an influence on neuro-inflammation

process, causing a depression and similar disorders.<sup>19</sup> In the other hand, IL-6 also influenced on neuro-degradation process through T helper (Th)-17 induction which frequently occurred on geriatrics, resulting in conditions susceptible to encounter depression.

## CONCLUSION

From the results of this study, it could be concluded that high serum IL-6 level increased the risk of depression in geriatric. Thus indicating a correlation between the increasing of IL-6 serum level with depression incidence.

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## AUTHOR CONTRIBUTION

All authors contributed in the manuscript, based on their contribution as: study proposal in general (Cokorda Wahyu [CW] and Tuty Kuswardhani [TK]), study design (CW, TK), statistical analysis (CW, TK), study running (CW, TK), manuscript writing (CW, TK). We confirmed that all authors have read and agreed to the content of this manuscript.

## CONFLICT OF INTEREST

This paper was written independently. All authors disclose no financial or personal relationships with other people or organizations that could inappropriately influence the work.

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