CrossMark

Relationship of albumin serum levels and Neutrophil-Lymphocyte Ratios (NLR) on activities of daily living elderly patients with delirium at Sanglah General Hospital, Bali, Indonesia

I Made Arya Winangun,[1] I Gusti Putu Suka Aryana,[2*] I Nyoman Astika,[2]
Raden Ayu Tuty Kuswardhani[2]

ABSTRACT

Background: Delirium often occurs to the elderly, which is associated with inflammation, malnutrition and low activities of daily living (ADL). The reduced ADL is associated with poor outcomes and death. ADL is affected by malnutrition and inflammation. Albumin is a marker for malnutrition and inflammation, while the neutrophil-lymphocyte ratio (NLR) is a marker for inflammation. This study aims to determine the relationship between albumin serum levels and NLR to ADL in elderly delirium patients in Sanglah Hospital Denpasar.

Methods: A cross-sectional correlative study among elderly delirium patients were conducted at Sanglah Hospital Denpasar from January to July 2018. The variables studied were albumin levels, NLR and ADL

scores. Data analysis using SPSS version 23 with Pearson or Spearman correlation tests to determine the relationship between the variables examined.

Results: Total of 73 patients were sampled. The average albumin levels were 3.35 gram/dL, the median NLR was 8.17 and the median ADL scores were 3. There was no significant relationship between albumin and ADL in elderly delirium patients (p=0.35, r=0.10), but a significant correlation was obtained between NLR and ADL scores (p=0.04, r=-0.24).

Conclusion: Albumin did not significantly affect ADL. NLR was negatively correlated with ADL. The higher the NLR, the lower the ADL of elderly delirium patients.

[1]Internal Medicine Department, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia
[2]Geriatric Division, Internal Medicine Department, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia

*Correspondence to:
I Gusti Putu Suka Aryana, Geriatric Division, Internal Medicine Department, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia
suka_aryana@unud.ac.id

INTRODUCTION

Delirium is still a problem that often occurs to the elderly. The incidence of delirium in the elderly is 1-2% in general populations, about 22% in patients undergoing hospitalization and reaching 80% in patients undergoing intensive therapy.[1] Delirium is associated with a mortality rate after admission about 25-33%.[2] The mortality rate of delirium is 14.2% in 1 month and it becomes 22.2% in 6 months.[3] The mortality rate is even higher with the presence of comorbid diseases accompanied by the severity of the diseases. The delirium is associated with unfavourable result conditions such as decreased permanent cognition, loss of independence and reduced mobility.[1,2,4]

Delirium is an acute confusional state characterized by changes in the level of consciousness, acute onset and fluctuations, reduced attention and disorganized thought.[1] Delirium is influenced by several factors, including predisposing factors and precipitating factors. Predisposing factors of delirium such as old age, cognitive impairment, ADL (activities of daily living), vision and hearing

problems, and comorbidity of disease.[5,6] Delirium precipitating factors are infection, stress, malnutrition and acute conditions such as electrolyte disturbances, dehydration, and hypoglycemia.[1,5,6] Malnutrition, inflammation and ADL impairment are several factors associated with the occurrence of delirium.

ADL reflects the primary functional status in elderly patients. ADL covers health care and personal hygiene, wearing clothes, mobilizing and eating.[7,8] Good functional activity of elderly patients is a long-term goal of comprehensive elderly care. The reduction of daily functional activity in patients undergoing hospitalization is associated with poor outcomes and death.[9] ADL is said to be affected by malnutrition and inflammation. Malnutrition causes reduced body protein and reduced muscle mass. Both of them were associated with disability and reduced physical activity.[10,11] Elderly patients with acute inflammation have lower muscle strength, lower absolute muscle mass and high ADL dependency.[12]

Elderly patients are susceptible to malnutrition, and inflammation.[10] Nutrition is very important, especially in the brain with high levels of nutritional and metabolic activity.[13] Deficiency in micronutrients and vitamins such as niacin and thiamine can affect delirium due to disruption of working neurotransmitters.[13] Lack of food intake, anorexia, lack of nutrition and inflammation with its cytokines can also cause a decrease in albumin levels.[10] Decreased albumin levels are not a physiological condition due to ageing.[10]

Albumin is one of the acute negative phase proteins.[14] Serum albumin is found low in conditions of malnutrition, infection and sepsis. Serum albumin said to be very sensitive to diagnose malnutrition in elderly patients that are hospitalized.[10] There is a concept of stress that causes the occurrence of hypoalbuminemia makes albumin as a marker for inflammation.[14] High albumin levels can be associated with short periods of hospitalization of patients, good functional status ability with short periods of rehabilitation.[10]

The neutrophil-lymphocyte ratio (NLR) is a marker that is being widely studied as a marker for systemic or chronic inflammation and oxidative stress.[4,15] The NLR is thought to be increased in delirium. The occurrence of inflammation and oxidative stress are thought to underlie the pathophysiology of delirium. Inflammation is also mentioned as an independent risk factor of disability, functional activity and mortality of elderly patients treated.[12] Inflammation is said to have a catabolic effect on muscles and inflammation that can reflect the presence of more severe and systemic diseases that affect muscle mass.[12]

Elderly delirium patients are prone to have more risk of inflammation and malnutrition than non-delirium patients. The occurrences of inflammation and malnutrition likely to be more affect the albumin levels and NLR.[4,16,17] Albumin and NLR are laboratory examination that routinely checked and easy to do. Both of these also mentioned as markers associated with malnutrition and inflammation. Based on the author's knowledge to date, there was no data that presents albumin and NLR of elderly patients in Bali and its ADL level. A good ADL score or improvement of ADL score during treatment can reduce the period of hospitalization and improve patient prognosis. Initial examination of albumin and NLR thought to provide an overview of ADL status of elderly delirium patients who are hospitalized, and it can be used as a simple initial guide in refining strategies, nutritional management, pharmacological therapy or other interventions to improve the primary functional status of elderly patients with delirium.

Based on those mentioned above, this study aims to determine the relationship between serum albumin levels and NLR to ADL in elderly patients with delirium in Sanglah Hospital Denpasar.

METHODS

Study design

The design of this study was a correlative cross-sectional study to determine the relationship between serum albumin levels and NLR to ADL of elderly delirium patients in Sanglah Hospital Denpasar. Cross sectional study was used as initial study design. This research was conducted from January to July 2018. Samples were collected through a consecutive sampling of patients that were hospitalized in Sanglah Hospital Denpasar which met inclusion and exclusion criteria. Inclusion criteria in this study were willing to participate in research, patients with delirium and elderly patients age >60 years. Elderly delirium patients were always accompanied by comorbidity and to represent a condition that happens in elderly delirium patients in common, the exclusion criteria in this study were patients with comorbidity malignancy including blood malignancy. The patient or patient's relative was asked for approval to take part in the study. Demographic data include age and gender was taken and a blood sample was collected.

Instruments and Measurements

Delirium patient was measured with the Confusion Assessment Method (CAM) Questionaire.[18] Hypoalbuminemia is an albumin serum level <3.5 gram/dL.[10,19] The NLR is the ratio of neutrophil per lymphocyte with a normal ratio of 0.78 to 3.53.[15] The higher the value of the lymphocyte neutrophil ratio indicates the higher of inflammation occurred. Assessment of albumin and NLR was carried out once while the patient hospitalized and taken through the patient's venous blood and analyzed in the Sanglah Hospital Denpasar laboratory.

ADL was measured with the Barthel Index Activity of Daily Living instrument which includes 10 questions.[7] Barthel Index includes daily activities such as eating, mobilizing such as changing attitudes from lying down to sitting, moving or walking, up and downstairs, and personal hygiene such as bathing, wearing clothes, controlling excretion, defecating, urinating, and using restrooms.[7] Barthel Index scores can be grouped into score of 0-4 indicating total dependency, score of 5-8 indicating heavy dependency, score of 9-11 indicating moderate dependency, score of 12-19 indicating mild dependency and score of 20 indicating independence. The

higher the total scores of the Barthel Index indicate the higher the level of patient independence.[7]

Statistical Analysis

The continues data was presented in the form of mean + SD if it had a normal distribution and in the form of median if it had an abnormal distribution. A normality test using the Kolmogorov-Smirnov was conducted in this study. Hypothesis testing used the Pearson correlation for normally distributed data or Spearman correlation when the data were not normally distributed. Statistical analysis was used to determine the correlation of serum albumin levels to ADL scores and the correlation of NLR to ADL scores. Data analysis was performed with the *Statistical Package for the Social Sciences* (SPSS) version 23 (IBM Corp., NY, USA) for Windows. The level of significance of this study was set at a probability value (p) of less than 0.05.

RESULTS

In this study, 73 samples met the inclusion and exclusion criteria, with 35 (47.9%) were male and 38 (52.1%) were female. The mean of patients age enrolled in this study was 73.49. The characteristics of the sample were listed in Table 1. Normality test was performed to determine the data distribution. Results of the normality test (Kolmogorov-Smirnov test) were normal data distribution for albumin serum levels and non-normal data distribution for NLR and ADL scores. There was hypoalbuminemia in elderly delirium patients in this study with the mean of albumin levels was 3.35 g/dl (Table 1). The median of leukocytes was 12.58 (5.41-57.68) × 10^3/µl, the median of neutrophils was 9.70 (3.67-43.66) ×10^3/µl, the median of lymphocytes was 1.24 (0.33-5.92) x10^3/µl and the median of NLR was 8.17 (1.38-63.11). The median of ADL scores was 3 (0-18) with most of the patients with ADL scores categories of total dependency (58.9%) (Table 1).

Table 1 Baseline Characteristics of Respondents

Variables	Respondents (N=73)
Age (years) (mean±SD)	73.49±7.84
Gender (%)	
Male	35 (47.9)
Female	38 (52.1)
Albumin levels, mean (g/dL) (mean±SD)	3.35±0.64
Leukocytes, median (10^3/µl)	12.58 (5.41-57.68)
Neutrophils, median (10^3/µl)	9.70 (3.67-43.66)
Lymphocytes, median (10^3/µl)	1.24 (0.33-5.92)
Neutrophil lymphocyte ratios, median	8.17 (1.38-63.11)
ADL scores, median	3 (0-18)
ADL scores categories (%)	
Total dependency	43 (58.9)
Severe dependency	11 (15.1)
Moderate dependency	10 (13.7)
Mild dependency	9 (12.3)

g: gram; dL: deciliter; µl: microliter; ADL: Activities of daily living; SD: standard deviation

Table 2 The Correlation Analysis between Albumin Serum Levels and Neutrophil Lymphocyte Ratios to ADL Scores

Variables	ADL scores	
	r	p
Albumin levels	0.10	0.35
Leukocytes	-0.08	0.46
Neutrophils	-0.10	0.38
Lymphocytes	0.28	0.013
NLR	-0.24	0.04

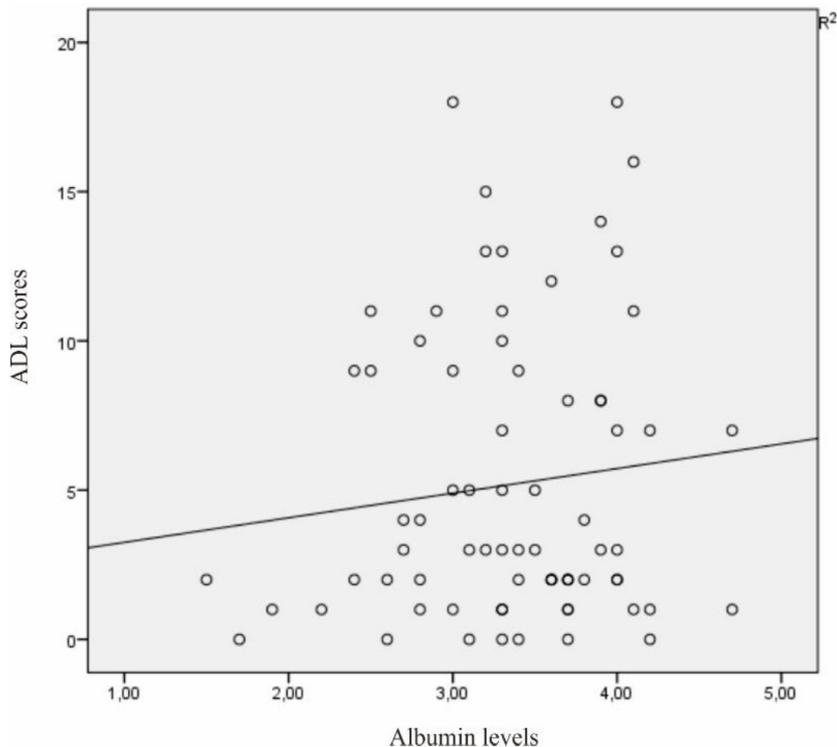ADL: activities of daily living; NLR: Neutrophil-Lymphocyte Ratio

Figure 1 Scatter Plot with No Correlation between Albumin Levels to ADL Scores of Elderly Delirium Patients
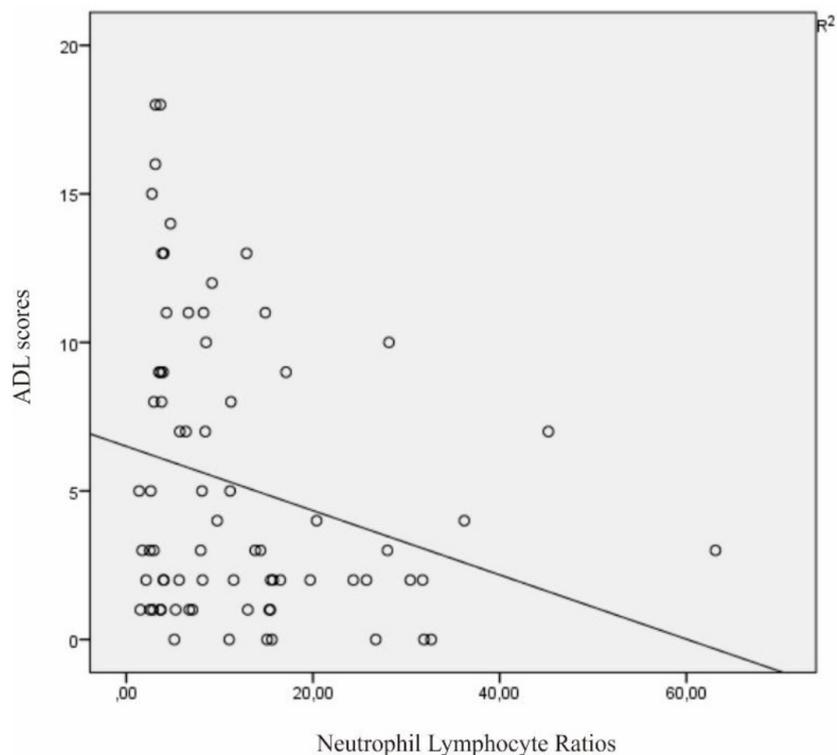

Figure 2 Scatter Plot with Negative Correlation between Neutrophil Lymphocyte Ratios to ADL Scores of Elderly Delirium Patients

The results of the correlation tests were listed in Table 2. There was no significant relationship between albumin levels and ADL scores of elderly delirium patients (p= 0.35, r= 0.10) as seen in scatter plot Figure 1, but found a significant relationship with a weak correlation between neutrophil lymphocytes ratios and ADL scores of elderly delirium patients (p= 0.04, r= -0.24) as seen in scatter plot Figure 2.

DISCUSSION

This study using a homogeneous population sample of elderly delirium patients. Elderly delirium patients were prone to a more condition of stress, inflammation and malnutrition and also likely to cause a decrease in albumin and an increase in the neutrophil-lymphocyte ratios (NLR).[4,16] Elderly patients with delirium are at risk of having low albumin levels and increased of NLR compared to non-delirium patients.[4,16] Albumin is a marker of malnutrition and inflammation while the NLR also mentioned as a marker for inflammation.[4,13] Conditions of stress, inflammation, malnutrition, and ADL functional activity impairment are factors related to delirium in the elderly.

In this study, there was no statistically significant the relationship between albumin levels and ADL scores in elderly patients with delirium. The results of this study differed from a cohort study of Kitamura et al. which stated that there was a significant correlation between decreasing albumin serum levels and decreasing total Barthel ADL Index scores.[20] Low albumin indicates malnutrition and reduced body protein. A decrease in body protein can cause a reduction in muscle mass also associated with disability and reduced physical activity. Loss of muscle mass is said to occur to patients with low albumin levels.[10] Kitamura et al. studied the relationship of albumin with ADL in a population of frail elderly patients, where frailty itself is a characteristic of low physical activity, reduced walking speed, exhaustion and poor endurance, whereas this study was in a population of elderly delirium patients. Albumin did not appear to be associated with ADL in elderly delirium patients. In Kitamura study, there was a significant relationship between albumin and ADL scores but still could not explain the causality between the two of them. Kitamura et al. further stated that other factors could affect albumin and ADL that had not been studied.[20] There are possibilities role of inflammation with inflammatory markers other than albumin.

Albumin is an acute negative phase protein and is widely used as a marker for inflammation.[9,14] Albumin has a half-life of 25 days with the synthesis of 10.5 gram/day and is maintained in balance through the kidneys, gastrointestinal and catabolic clearance.[14,19] Albumin serum has some protective properties by maintaining the physiological

homeostasis of the body and inhibiting the progression of pathological conditions.[9] Albumin provides >50% of total antioxidant in the body's plasma by digesting free radicals such as nitric oxide and binding to unconjugated bilirubin.[19]

Some sources mention that albumin as a marker for malnutrition, but according to Levitt et al., albumin has a poor correlation as a marker for malnutrition.[19] Under dietary conditions and starvation for up to 6 months or in chronic anorexia nervosa conditions, a drastic reduction in calories causes the protein to be released from the tissue from breaking down of the tissue muscle but still with an amount sufficient enough to maintain normal albumin serum levels.[19] Villafane et al. mentioned that malnutrition, as measured by MNA-SF (Mini Nutritional Assessment-Short Form), was significantly associated with low functional status Barthel Index ADL.[11] Malnutrition can affect the activity of the muscular and nervous system.[11] Malnutrition affects the gait and balance due to brain weakness and inability to associate sensorimotor and cognitive needs.[11] Direct nutritional assessment such as through MNA-SF seems to be more able to assess the state of malnutrition than through serum albumin levels.

Hypoalbuminemia occurs due to increased albumin capillary permeability which leads to redistribution of albumin from the vascular to interstitial space.[19] Hypoalbuminemia due to chronic inflammation occurs due to decreased albumin syntheses in the liver.[19] Decreased albumin can also occur to a low-protein diet. A condition that can affect albumin levels come from diseases that increase protein catabolism or changes from liver metabolism that causes a decrease in albumin synthesis.[10] Thus, albumin levels are primarily influenced by conditions such as liver disease, kidney disease, trauma, burns, cancer, and other inflammatory processes.[9,14] In this study, there was no significant relationship between albumin levels and ADL scores. Factors that influence albumin due to diseases affecting albumin levels must be controlled for another research.

In this study, a significant correlation was obtained between NLR to the ADL scores of elderly patients with delirium. An increase in NLR correlated with a decrease in ADL scores. The result of this study was similar to Putri et al. with a significant correlation between NLR to the Barthel ADL index.[17] Putri et al. tested the NLR to patients with ischemic stroke, with another inflammatory marker used were hs-CRP (high sensitivity C-Reactive Protein). Hs-CRP also had a significant correlation to the Barthel ADL Index in patients with ischemic stroke.[17] When compared the NLR and hs-CRP, there was no significant difference in accuracy between the NLR and hs-CRP to predict the outcome of patients with acute ischemic stroke.[17]

Disturbances in the blood-brain barrier underlie the mechanism of delirium.[4] In systemic inflammatory conditions, neutrophils bind to endothelial cells from the blood-brain barrier, then migrate across the barrier and release reactive oxygen species and protease.[4] An increased permeability of the blood-brain barrier with cytokines enters brain, is thought to activate microglia which then causes another inflammation and oxidative stress in the brain.[4]

Inflammation is one of the mechanisms underlying delirium with its cytokines and other inflammatory responses that have been widely studied.[4] The body's defence system had an innate immune system and adaptive immune system response when inflammation occurred.[21] Neutrophils act as an immune system that directly plays a role when an infection occurs, while lymphocytes are involved as an adaptive immune system response.[21] In stressful situations, the body's physiological response to an increment of neutrophils and reduction of lymphocytes.[4,21] Neutrophils are the first line of defence during inflammation, when activated, releasing reactive oxygen species, myeloperoxidase and proteolytic enzymes to destroy pathogen or damaged cells.[4] Lymphocytes can be reduced in acute stress conditions due to increased cortisol and catecholamines then undergoing redistribution to lymphatic tissue.[4]

The NLR is a marker for inflammation that is being widely studied. The NLR reflects the systemic inflammation and oxidative stress of delirium patients.[4] The NLR can indicate the inadequate immune system response and oxidative stress that might occur in the pathophysiology of delirium.[4] In this study, neutrophils levels alone did not correlate with ADL delirium patients, while lymphocyte levels were significantly related to the ADL delirium patients. However, based on Egberts et al., neutrophils and lymphocytes when standing alone did not significantly refer to delirium.[4] The NLR is thought to be an integrated balance of the two components of the immune system into one marker.[4] The NLR increases especially in conditions of infection and sepsis compared to non-sepsis.

Inflammation is said to be an independent risk factor of disability, impairment functional activity and mortality of elderly patients.[12] Increased NLR is associated with decreased functional status Barthel ADL Index of elderly patients. Liu et al. mentioned that elderly patients with acute inflammation had lower muscle strength, lower absolute muscle mass and higher dependence of

ADL.[12] Increased inflammation marker of CRP (C-Reactive Protein) were also associated with decreased strength of handgrip and reduced muscle mass compared to normal CRP levels.[12] Inflammation is said to have a catabolic effect on muscles and inflammation that can reflect the presence of more severe and systemic disease that affects muscle mass.[12]

Albumin did not correlate with the functional status of ADL, in contrast to the NLR which correlated significantly to the functional status of ADL. Neutrophil lymphocyte ratio is a simple routine laboratory examination. Neutrophil lymphocyte ratio can be used as a simple initial guideline on determining strategies and interventions for the functional status of elderly patients who are hospitalized. Clinicians should be able to consider factors that can be modified in preventing the reduction of ADL in elderly patients and should improve the functional status of ADL in elderly patients to carry out more independent activities in the future.

CONCLUSION

Albumin did not significantly affect ADL in elderly patients with delirium. The neutrophil-lymphocyte ratios were significantly correlated with the ADL of elderly patients with delirium. This study indicates that the higher neutrophil-lymphocyte ratios correlate to the lower the ADL functional status of elderly patients with delirium.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this study.

ETHICAL CONSIDERATION

Ethical approval for this study has been received from the Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia.

FUNDING

AUTHOR CONTRIBUTION

REFERENCES

1. Cerveira CCT, Pupo CC, Santos SDS, Santos JEM. Delirium in the elderly: A systematic review of pharmacological and non-pharmacological treatments. Dement Neuropsychol. 2017;11(3):270-275.
2. Lima DP, Ochiai ME, Lima AB, Curiati JAE, Farfel JM, Filho WJ. Delirium in hospitalized elderly patients and post-discharge mortality. Clinics (Sao Paulo). 2010;65(3):251-255.
3. Adamis D, Treloar A, Darwiche FZ, Gregson N, Macdonald AJD, Martin FC. Association of delirium with in-hospital and in 6-months mortality in elderly medical inpatients. Age Ageing. 2007;36(6):644-649.
4. Egberts A, Mattace-Raso FU. Increased neutrophil-lymphocyte ratio in delirium: a pilot study. Clin Interv Aging. 2017;12:1115-1121.
5. Soejono CH. Sindrom Delirium (Acute Confusional State). In: Buku Ajar Ilmu Penyakit Dalam Jilid III, 6th Edition: Siti Setiati et al (editors). Jakarta: Interna Publishing. 2015. p. 3798-3803.
6. Kuswardhani T, Sugi YS. Factors Related to the Severity of Delirium in the Elderly Patients with Infection. Gerontol Geriatr Med. 2017;3:1-5
7. Katz PP. Measures of Adult General Functional Status: The Barthel Index, Katz Index of Activities of Daily Living, Health Assessment Questionnaire (HAQ), MACTAR Patient Preference Disability Questionnaire, and Modified Health Assessment Questionnaire (MHAQ). Arthritis & Rheumatism (Arthritis Care & Research). 2003;49(S5):15-27.
8. Mlinac ME, Feng MC. Assessment of Activities of Daily Living, Self-Care, and Independence. Arch Clin Neuropsychol. 2016;31(6):506-516.
9. Hsu HY, Hwang LC, Lin CH, Lin CJ, Tjung JJ. Impact of Serum Albumin on Functional Status and Hospital Outcome in Oldest-Old Inpatients. International Journal of Gerontology. 2015;9(4):220-222.
10. Cabrerizo S, Cuadras D, Gomez-Busto F, Artaza-Artabe I, Marin-Ciancas F, Malafarina V. Serum Albumin and Health in Older People: Review and Meta Analysis. Maturitas. 2015:8(1):17-27.
11. Villafane JH, Pirali C, Dughi S, Testa A, Manno S, Bishop MD, et al. Association between malnutrition and Barthel Index in a cohort of hospitalized older adults article information. J Phys Ther Sci. 2016;28(2):607-12.
12. Liu JYJ, Reijnierse EM, Ancum JMV, Verlaan S, Meskers CGM, Maier AB. Acute inflammation is associated with lower muscle strength, muscle mass and functional dependency in male hospitalised older patients. PLoS One. 2019;14(4): e0215097
13. Sugita Y, Miyazaki T, Shimada K, Shimizu M, Kunimoto M, Ouchi S, et al. Correlation of Nutritional Indices on Admission to the Coronary Intensive Care Unit with the Development of Delirium. Nutrients. 2018;10(11):1-12.
14. Bharadwaj S, Ginoya S, Tandon P, Gohel TD, Guirguis J, Vallabh H, Jevenn A, Hanouneh I. Malnutrition: Laboratory Markers vs Nutritional Assessment. Gastroenterol Rep (Oxf). 2016;4(4):272-280.
15. Prabawa IPY, Bhargah A, Liwang F, Tandio DA, Tandio AL, Lestari AAW, et al. Pretreatment Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as a Predictive Value of Hematological Markers in Cervical Cancer. Asian Pac J Cancer Prev. 2019;20(3):863-868.
16. Kim H, Chung S, Joo YH, Lee JS. The major risk factors for delirium in a clinical setting. Neuropsychiatr Dis Treat. 2016;12:1787-93.

17. Putri TL, Ganie RA, Rambe AS. Neutrophil-Lymphocyte Ratio and High Sensitivity C-Reactive Protein as Ischemic Stroke Outcome Predictor. Indonesian Journal of Clinical Pathology and Medical Laboratory. 2017;23(3):240-245.
18. Vietara DW. Uji Kesahihan dan Keandalan Algoritma Confusion Assessment Method sebagai Instrumen Penapis Delirium Lanjut Usia di Instalasi Gawat Darurat RSUPN Dr. Ciptomangunkusumo [Thesis]. Universitas Indonesia. 2012.
19. Levitt DG, Levitt MD. Human Serum Albumin Homeostasis: A New Look at the Roles of Synthesis, Catabolism, Renal and Gastrointestinal Excretion, and the Clinical Value of Serum Albumin Measurements. Int J Gen Med. 2016;9:229-55.
20. Kitamura K, Nakamura K, Nishiwaki T, Ueno K, Nakazawa A, Hasegawa M. Determination of whether the Association between Serum Albumin and Activities of Daily Living in Frail Eldery People is Casual. Environ Health Prev Med. 2012;17(2):164-168.
21. Djordjevik D, Rondovic G, Surbatovik M, Stanojevic I, Udovicic I, Andjelic T, et al. Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio and Mean Platelet Volume-to-Platelet Count Ratio as Biomarkers in Critically Ill and Injured Patients: Which ratio to Choose to Predict Outcome and Nature of Bacteremia?. Mediators Inflamm. 2018:1-15.