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Older age and worse nutritional state were related with impaired inflammatory response in elderly patients

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ABSTRACT

Background: Ageing process is related with multisystem disorders. One of them is immune response impairment. It is imperative to evaluate the association between age and related nutritional status with inflammatory response in elderly patient.

Methods: A cross sectional study to evaluate inflammatory response among elderly patients (≥60 years) at Geriatric Out-patient Clinic, Sanglah Hospital was conducted. Seventy-two patients were enrolled in the study. Age, nutritional states (body mass index and mini nutritional assessment), and inflammatory markers (interleukin-2 [IL-2] and C-reactive protein [CRP]) and other anthropometric as well as laboratory parameters were measured in the study.

Results: In the study, it was revealed that age has a moderately negative correlation with both of plasma IL-2 and serum CRP levels (R= -0.305, p=0.009; and R= -0.413, p=0.005, respectively). Plasma IL-2 levels were positively correlated with several variables like body mass index (R=0.282, p=0.016), mini nutritional assessment (R=0.237, p=0.045), biceps skin fold (R=0.291, p=0.013), and triceps skin fold (R=0.258, p=0.028). While serum CRP levels has positive correlation with lying diastolic blood pressure (R=0.345, p=0.020) and negative correlation with calf circumference (R=-0.312, p=0.037). No significant associations were found between diabetes and hypertension with inflammatory markers.

Conclusion: This study concluded that older age and worse nutritional state were related to worse inflammatory response in the elderly patients.

Keywords: Elderly, Nutritional State, Inflammatory Response

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INTRODUCTION

Since the survival of population has been increasing due to improvement of quality of life style and health care system, the elderly population is increasing almost in all countries in the world. Globally, the number of older people (aged 60 years or over) is expected to be more than double, from 841 million people in 2013 to more than 2 billion in 2050. Older people are projected to exceed the number of children for the first time in 2047. By 2050, nearly 8 out of 10 of the world's older population will live in the less developed regions.[1]

Based on Statistic Bureau of Indonesia, the prevalence of population over 60 years in 2014 is 8.03%. It is predicted that in 2015 will be 8.5% and reach 10.0% by 2020. Bali is the top 4 of the highest prevalence of the elderly among all provinces in Indonesia (10.05%) after Yogyakarta (13.05%), Central Java (11.11%), and East Java (10.96%).[2] However, as consequence, the incidence and prevalence of some aging-related diseases are also increased, causing ever increased health and social problems.

Body weight tends to increase until around 60 years of age and then will be decreasing steadily in line with age. Body weight and metabolic syndrome were lower in elderly compared to younger age, although the prevalence of diabetes was still consistently higher in elderly.[2] Nutritional state can be measured by some parameters, such as body mass index, waist circumference or mini nutritional assessment (MNA). The Mini Nutritional Assessment has recently been designed and validated to provide a single and rapid assessment of nutritional status in elderly patients. The MNA test is composed of simple measurements and brief questions that can be completed in about 10 minutes. Discriminatory analysis was used to compare the findings of the MNA with the nutritional status determined by physicians, using the standard extensive nutritional assessment including complete anthropometric, clinical biochemistry, and dietary parameters.[4]

Generally, chronic inflammation is a characteristic feature of aging in which inflammatory state is found predominantly among the elderly. Human polynucleotide phosphorylase might play a significant role in producing pathological changes

Table 1 Baseline Characteristic of Patients

Variables	N	Mean	Standard deviation
Age (year)	72	72.06	6.93
Body fat (%)	72	31.09	7.94
Visceral fat (Scale, 1-15)	72	9.22	6.96
Resting metabolic rate (kcal)	72	1241.93	252.71
Body mass index (kg/m^2)	72	21.99	3.98
Standing systolic blood pressure (mmHg)	72	136.27	18.26
Standing diastolic blood pressure (mmHg)	72	79.1	11.43
Sitting systolic blood pressure (mmHg)	72	136.51	19.45
Sitting diastolic blood pressure (mmHg)	72	76.4	8.72
Lying systolic blood pressure (mmHg)	72	134.33	21.83
Lying diastolic blood pressure (mmHg)	72	74.29	8.88
Standing Pulse rate (x/minute)	72	82.99	9
Sitting pulse rate (x/minute)	72	79.81	8.42
Lying pulse rate (x/minute)	72	77.03	8.47
Body-age (year)	72	60.64	13.4
Whole body Subcutaneous fat (%)	72	23.71	7.51
Trunk subcutaneous fat (%)	72	21.4	7.14
Arm subcutaneous fat (%)	72	35.12	12.31
Leg subcutaneous fat (%)	72	30.76	10.08
Whole body skeletal muscle (%)	72	24.03	4.35
Trunk skeletal muscle (%)	72	7.92	4.51
Arm skeletal muscle (%)	72	28.74	6.16
Leg skeletal muscle (%)	72	38.27	6.56
Forearm circumference (cm)	72	25.76	3.59
Calf circumference (cm)	72	32.53	3.95
Biceps skinfold (mm)	72	4.81	1.16
Triceps skinfold (mm)	72	4.09	1.22
White blood cells(103/µL)	72	7.39	2.7
Neutrophils(103/µL)	72	4.31	2.14
Lymphocytes (103/µL)	72	2.14	0.9
Monocytes (103/µL)	72	0.47	0.17
Hemoglobin (g/dL)	72	12.55	1.48
Hematocrit (%)	72	39.23	4.86
Thrombocytes(103/µL)	72	256.7	71.96
SGOT (mg/dL)	46	26.53	15.97
SGPT (mg/dL)	46	23.14	20.97
Serum albumin (g/dL)	72	3.68	0.65
Blood urea nitrogen (mg/dL)	46	16.14	7.38
Serum creatinine (mg/dL)	46	0.95	0.41
Plasma Interleukin-2 (pg/mL)	72	8.4	5.47
Serum C-reactive protein (mg/L)	45	4.01	5.78
Mini nutritional assessment (score)	72	21.57	4.29
Activity daily living (score)	72	18.21	3.99

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

associated with aging by generating pro-inflammatory cytokines via reactive oxidative stress and NF-κB.[5] NF-κB play an important role in inflammatory reaction related with aging process.[6,7] As increasing age usually accompanied by decreasing in physical performance and immune system, the presence of a less competent immune system is exerting a great influence on the age-related morbidity and mortality due to the increase of susceptibility to infectious disease, autoimmune processes, and cancer.[8]

The purpose of the study is to evaluate the relationship of age and nutritional state with inflammatory response among the elderly people.

MATERIAL AND METHODS

A cross sectional study on inflammatory response among elderly patients (over 60 years) at Geriatric Out-patient Clinic, Sanglah Hospital was conducted. Seventy-two patients were enrolled in the study. Patients with acute and/or severe illness such as acute or severe infection, acute or severe liver diseases, acute cardiovascular events, and acute or severe kidney diseases, immune-compromised, and malignancies, were excluded.

Several variables were measured in the subjects namely age, nutritional state (body mass index [BMI], MNA), anthropometric state, and laboratory parameter: blood routine (white blood cells, neutrophils, lymphocytes, monocytes, hemoglobin, hematocrit, thrombocytes), liver function (serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], serum albumin), renal function (blood urea nitrogen [BUN], and serum creatinine [SC]) and inflammation markers (plasma interleukin-2 [IL-2] and serum C-reactive protein [CRP]).

Body mass index was measured by standard formula (kg/m^2). In case a patient could not stand up, body height is calculated by formula as follow: for woman, height = (1.83 × knee height in cm) -(0.24x age in year) + 84.88 cm; and for man, height = (2.02 × knee height in cm) - (0.24x age in year) + 64.19 cm. Mini nutritional assessment, a single and rapid assessment of nutrition state in elderly, was measured by questionnaire that had been proposed by Vellas et al. (1999)[3]. The sum score between 0-30, which the lower score reflects the worse nutrition state (adequate nutritional status, MNA ≥ 24; at risk of malnutrition, MNA between 17 and 23.5; and protein-calorie malnutrition, MNA < 17). Anthropometric measurement (body fat, visceral fat, subcutaneous fat, skeletal muscle, resting metabolic rate, body age) was measured by bioelectric impedance method (Karada Scan™, Body Composition Monitor

Table 2 Correlation of Several Variables with IL-2 and CRP

Variables	IL-2		CRP	
	R	p	R	p
Age	-0.305	0.009*	-0.413	0.005*
Body fat	-0.026	0.828	-0.047	0.76
Visceral fat	0.211	0.075	-0.138	0.368
Resting metabolic rate	0.192	0.106	-0.201	0.185
Body mass index	0.282	0.016*	-0.178	0.241
Standing systolic blood pressure	-0.074	0.536	0.035	0.822
Standing diastolic blood pressure	0.1	0.403	0.206	0.174
Sitting systolic blood pressure	0.033	0.785	0.097	0.528
Sitting diastolic blood pressure	0.104	0.385	0.164	0.281
Lying systolic blood pressure	-0.039	0.743	0.128	0.402
Lying diastolic blood pressure	0.176	0.14	0.345	0.020*
Standing Pulse rate	-0.039	0.743	0.251	0.402
Sitting pulse rate	-0.029	0.81	0.197	0.097
Lying pulse rate	-0.083	0.488	0.169	0.194
Body-age	0.056	0.64	-0.269	0.074
Whole body Subcutaneous fat	0.064	0.593	0.005	0.719
Trunk subcutaneous fat	0.066	0.58	-0.019	0.904
Arm subcutaneous fat	-0.017	0.886	0.098	0.522
Leg subcutaneous fat	0.062	0.605	0.108	0.479
Whole body skeletal muscle	0.086	0.474	-0.001	0.995
Trunk skeletal muscle	0.041	0.73	0.033	0.83
Arm skeletal muscle	0.039	0.748	-0.061	0.692
Leg skeletal muscle	0.142	0.233	-0.104	0.499
Forearm circumference	0.115	0.335	-0.191	0.21
Calf circumference	0.079	0.511	-0.312	0.037*
Biceps skinfold	0.291	0.013*	-0.192	0.207
Triceps skinfold	0.258	0.028*	-0.167	0.272
Serum albumin	0.168	0.158	-0.241	0.111
Blood urea nitrogen	0.221	0.139	-0.026	0.864
Serum creatinine	-0.087	0.566	-0.056	0.714
Mini nutritional assessment	0.237	0.045*	0.004	0.981
Activity daily living	0.076	0.527	-0.294	0.05

HBF-375, OMRON), and skinfold was measured by skinfold caliper baseline® DME 43063.Barthel Index of Activities of Daily Living (ADL) was used to score ADL.

Plasma IL-2 levels was measured by Elisa procedure with reagent Quantikine. Serum CRP level was measured by spectrophotometric procedure (Cobas C501) with reagent Roche. Diabetes is diagnosed by criteria of diabetes of American Diabetes Association (2014)[9] and hypertension was confirmed if blood pressure was ≥ 140/90 mmHg (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).[10]

Statistical tests were used to analyze the data in the study including descriptive presentation. Spearman rho correlation test was used to analyze the correlation of several variables with IL-2 and CRP since IL-2 and CRP showed abnormal distribution after being analyzed using K-S test; Mann-Whitney U test was used to differentiate the levels of serum IL-2 and CRP among patients with and without diabetes and with and without hypertension. One way anova was used to differentiate the levels of IL-2 and CRP among categorical of age, BMI and MNA. Significant value is confirmed if $p<0.05$. The study was approved by Ethical Clearance Committee, Research and Development Unit, Faculty of Medicine Udayana University/ Sanglah Hospital, Denpasar, No: 988/UN.14.2/ Litbang/2013.

RESULTS

A cross sectional study enrolling 72 elderly patients (≥60 years old) at Geriatric Out-patient Clinic, Sanglah Hospital was conducted. Men to women ratio were 30/42 (41.7%). The baseline characteristics of subjects are depicted in Table 1. We categorized subject's age into 3 groups namely 60-69 years, 70-79 years, and 80 years or over and we found the prevalence of each group is 30 (41.7%), 29 (40.3%), and 13 (18.0%), respectively. Based on MNA, it was found that 9 (12.5%) subjects were categorized as protein and calorie malnutrition, 32 (44.4%) subjects with malnutrition risk, and 31 (43.1%) subjects with adequate nutrition status. Twenty-five out of 72 (34.7%) patients had hypertension and 17 out of 72 (23.6%) patients had type 2 diabetes mellitus.

Plasma IL-2 and serum CRP levels were used as markers of inflammatory response among the elderly patients. The correlation between several variables and inflammatory response can be seen in Table 2, Figure 1A and Figure 1B. This study reveals that age has negative correlation with both of plasma IL-2 and serum CRP levels (R= -0.305, p=0.009; and R= -0.413, p=0.005, respectively). Plasma IL-2 level has positive correlation with several variables i.e. BMI (R=0.282, p=0.016), MNA (R=0.237, p=0.045), biceps skin fold (R=0.291, p=0.013), and triceps skin fold (R=0.258, p=0.028). While serum CRP level has positive correlation with lying diastolic blood pressure (R=0.345, p=0.020) but negative correlation with calf circumference (R= -0.312, p=0.037). The correlation between age and CRP seems stronger than between age and IL-2 (Figure 1A). Body mass index and MNA showed similar correlation with IL-2 (Figure 1B). By decade

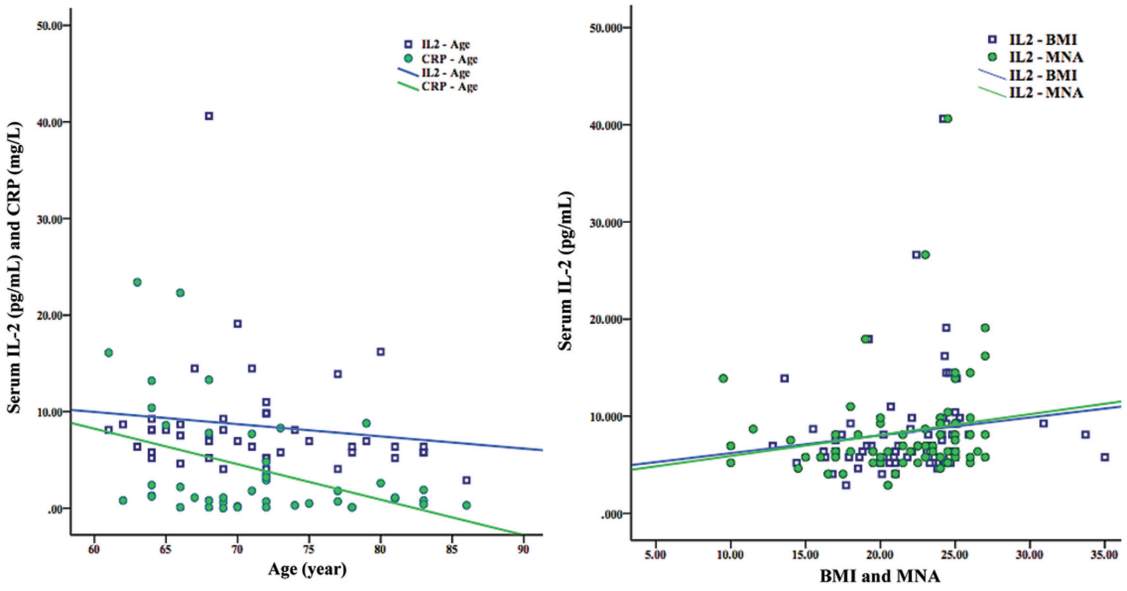

Figure 1 A. Correlation between Age and IL-2 and CRP. B. Correlation between BMI and MNA and IL-2.

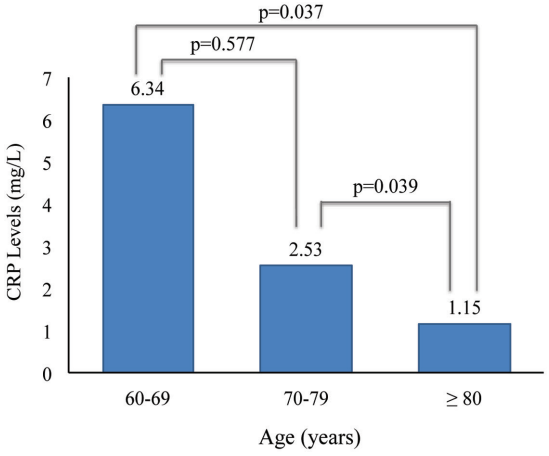

Figure 2 CRP Levels by Groups of Age

of age, it was found that although the absolute level of IL-2 was the lowest among 80 years or over and the highest among the group of 60-69 years, the statistical difference was not significant (6.63±3.18 vs. 7.90±3.60 vs. 9.64±7.30 pg/mL). Otherwise the CRP levels in the group of 80 years of age or over and 70-79 years revealed significantly lower than those with the group of 60-70 years of age (1.15±0.82 mg/L*vs.*2.53±2.98 mg/L*vs.* 6.34±7.64 mg/L; p=0.577, p=0.037 and 0.039, respectively) (Figure 2). The study also showed that there was no any significant difference of plasma IL-2 levels among each of 3 groups of nutrition states both by BMI (underweight vs. normal weight vs. overweight/obese, 6.98±2.72 *vs.* 8.70±6.43 *vs.* 8.73±2.35 pg/mL) and MNA (protein-calorie malnutrition *vs.* malnutrition risk *vs.* adequate nutritional status, 6.94±2.97 vs. 7.59±4.33 vs. 9.65±6.78 pg/mL).

Hypertension and diabetes are frequently associated to immune response impairment.

However, we found no significant difference between plasma IL-2 and serum CRP levels with and without hypertension (8.66±7.15 vs. 8.26±4.41 pg/mL, p=0.953; 3.65±4.83 vs. 4.29±6.53 mg/L, p=0.900, respectively). The plasma IL-2 level among patients with type 2 diabetes was also not significantly different compared to patients without diabetes (7.89±5.19 *vs.* 8.55±5.58 pg/mL, p=0.631). The same finding also showed for serum CRP levels (4.29±5.81 *vs.* 3.85±5.86 mg/L, p=0.413).

DISCUSSION

Among seventy-two elderly people, which 25 of them have got hypertension and 17 have diabetes, were enrolled in this study. This study revealed that advanced age and worse nutritional status were associated with immune response impairment which is determined by low level of plasma IL-2 and serum CRP.

Decrease IL-2 production was observed in cell culture from elderly individuals in response to some stimuli (PHA, PHA plus PMA, cross-linked anti-CD3 mAb OKT3 plus PMA, or PMA plus ionomycin). Age-related impairments in the activation of AP-1 and NF-AT are closely associated with decreased expression of IL-2.[11] Results of several studies on IL-2 production was evaluated and it showed that an age-related decrease was observed in 11 out of 14 studies in which PBMC or whole blood from young and elderly subjects were stimulated with PHA.[12] Our finding was similar to almost other study which showed the decreased level of plasma IL-2 with age. In this study, at least there were two important factors related with lower level

of IL-2: those with older age and worse nutritional state (BMI, MNA, biceps and triceps skin fold).

This study showed that CRP has negative correlation with age and with calf circumference (might be one of the indicators of lower physical performance or worse nutritional state). Similar to this study, a study by Yoshida et al. showed that serum CRP has negative correlation with physical performance in community-indwelling elderly in Japan.[13] It is different from our finding that levels of CRP was highest among 6th decade group and lowest among 8^{th+} decade group (Figure 2); a population study in Brazil showed that there was no difference of CRP levels among 6th, 7th and 8th+ decade group.[14] A community-based study by Yang et al. has reported that obesity and sarcopenic obesity are associated with increased levels of serum hs-CRP among Chinese older males.[15] A study by Santos et al. showed that increasing severity of metabolic syndrome is associated with increasing CRP. Central obesity was proved to be a major determinant of the low grade chronic inflammation in metabolic syndrome.[16] Those findings are different from our study that revealed no significant correlation between nutritional status reveals with CRP levels. However, the finding could not explain exactly why lying diastolic blood pressure has positive correlation and calf circumference has negative correlation with CRP levels.

Diabetes and hypertension are frequently associated with chronic inflammation as well as in metabolic syndrome.[16,17,18] However, in this study, there is no significant differences of IL-2 and CRP level among subjects with and without diabetes and hypertension. At least, in the population, inflammatory response in elderly patients was not influenced by existing diabetes and hypertension. Therefore, age and nutritional state were more dominant factors that influence inflammatory response in the elderly.

CONCLUSION

From the result of this study, it can be concluded that the older ages and worse nutritional state (expressed by body mass index and mini nutritional assessment) were related with worse inflammatory response in the elderly patients. However, further research is needed in order to prove whether improving nutritional status could also improve inflammatory response in elderly patients.

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AUTHOR CONTRIBUTION

All authors contributed in the manuscript, based on their contribution as: study proposal in general (Tuty Kuswardhani [TK], Gede Sukrawan [GS], Ketut Suastika [KS]), study design (TK, GS, KS), statistical analysis (KS), study running (TK, GS, KS), manuscript writing (TK, GS, KS). 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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