Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Sep 30; 10(B):2337-2344.
https://doi.org/10.3889/oamjms.2022.10626
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Nephrology*

The Correlation of Interleukin-6, Malnutrition Inflammation Score and Asymmetric Dimethylarginine in Chronic Kidney Disease Patients Undergoing Routine Hemodialysis

Stella Palar[1], Frans Erwin Wantania[2], Hanna Honoris[3]*

[1]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University, Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia; [2]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University, Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia; [3]Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University, Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia

Edited by: Ksenija Bogoeva-Kostovska
Citation: Palar S, Wantania EF, Honoris H. The Correlation of Interleukin-6, Malnutrition Inflammation Score and Asymmetric Dimethylarginine in Chronic Kidney Disease Patients Undergoing Routine Hemodialysis. Open Access Maced J Med Sci. 2022 Sep 30; 10(B):2337-2344. https://doi.org/10.3889/oamjms.2022.10626
Keywords: Interleukin-6; Malnutrition inflammation score; Asymmetric dimethylarginine; Chronic kidney disease; Hemodialysis
***Correspondence:** Hanna Honoris, Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University, Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia. E-mail: hhonoris@yahoo.com
Received: 28-Jul-2022
Revised: 10-Aug-2022
Accepted: 20-Sep-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Chronic kidney disease (CKD) patients undergoing routine hemodialysis (HD) have a high prevalence of protein-energy malnutrition (PEM) and inflammation. The combination of inflammation and PEM is associated with cardiovascular disease and poor outcomes. Interleukin-6 (IL-6) is an inflammatory factor that runs parallel to endothelial damage and is closely related to the nutritional status of CKD HD patients. The tool to assess nutrition status is malnutrition inflammation score (MIS) and to assess endothelial damage is asymmetric dimethylarginine (ADMA). It is currently unclear whether there is a correlation between inflammation, malnutrition, and endothelial dysfunction.

AIM: The aim of this study is to determine the correlation between IL-6, MIS, and ADMA in CKD HD patients.

METHODS: A cross-sectional design with analytic observational study was conducted on end stage renal disease patient who undergo routine hemodialysis for at least 2 years with the duration of hemodialysis is 4−5 h and at least twice per week. IL-6 was examined by kit (ELISA) and ADMA using LC-MS/MS at a certified laboratory in Manado city. History taking and physical examination were used to calculate MIS. Data analysis was done using SPSS version 22.

RESULTS: There were 30 participants consisting of 22 men (72%) and 8 women (28%). The median age of the subjects was 56.50 years. There was a statistically significant positive correlation between IL-6 and ADMA (r = 0.440, p = 0.015), MIS and ADMA (r = 0.378, p = 0.039), and IL-6 and MIS (r = 0.682, p = 0.0001).

CONCLUSION: There was a significant correlation between IL-6, MIS, and ADMA.

Introduction

Chronic kidney disease (CKD) has become a major health problem globally, with 2–3% of the country's assets spent on treating late-stage kidney disease [1]. The most important cause of death in hemodialysis (HD) patients is cardiovascular disease, and about 50% of deaths are related to cardiovascular disease [2], [3]. Studies have shown a correlation between protein energy malnutrition (PEM) or malnutrition with cardiovascular disease and increasing cardiovascular-related mortality rates [4].

Inflammation in CKD occurs due to kidney disorders that cannot excrete pro-inflammatory cytokines, uremic toxins, oxidative stress, comorbid diseases, and dialysis procedures. Pro-inflammatory cytokines interleukin-6 and asymmetric dimethylarginine were significantly increased in CKD HD patients and are significantly increased in CKD HD patients and are involved in the nutritional status [5].

Malnutrition and inflammation cause inflammatory malnutrition syndrome, which increase the risk of atherosclerosis in CKD patients undergoing HD [6]. Endothelial dysfunction is the basis of atherosclerosis formation, which occurs in the early stages of CKD patients and increases further with the progression of kidney disease. One of the markers of endothelial dysfunction is ADMA [7]. Levels of circulating ADMA are directly and significantly associated with CRP and IL-6, suggesting that inflammation and endothelial dysfunction are parallel processes in end-stage CKD patients [8], [9].

The recommended examination of protein-energy nutrient status by the Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) is a malnutrition inflammation score (MIS). MIS appears to be a comprehensive and significant assessment system associated with possible hospitalization, death, nutritional status, inflammation, and anemia in hemodialysis patients [10]. MIS values predict mortality rates in CKD patients with HD equivalent to

serum IL-6 and even higher than serum C-reactive protein (CRP) [11].

This study aimed to determine the correlation between IL-6, MIS, and ADMA in chronic kidney disease patients undergoing routine hemodialysis.

Methods

This study was an analytical observational study with a cross-sectional design. This research was conducted at the Hemodialysis unit of Prof. Dr R. D. Kandou Hospital, Manado, Indonesia, from August 2021 to December 2021. This study was approved by local ethics committee with the number: No.111/EC/KEPK-KANDOU/VII/2021.

Population and sampling

The population included in this study were all patients who underwent routine hemodialysis at Prof. Dr R. D. Kandou Hospital, Manado, Indonesia who met the inclusion and exclusion criteria.

Inclusion criteria were CKD patients who undergo routine hemodialysis for at least 2 years with 4−5 h duration and at least twice per week session, aged 18−60 years old and were willing to participate in the study. Exclusion criteria were the presence of malignancy, severe infection or sepsis, autoimmune diseases and congestive heart failure. The sampling method was carried out by consecutive sampling.

Interleukin-6 (IL-6) examination

Five milliliter of blood was drawn from the peripheral vein and measurements were taken using the enzyme-linked immunosorbent assay (ELISA) kit (Elecsys, cat. No 05109442190 from Roche Diagnostics International Ltd, Rotkreuz, Switzerland). The reference value of IL-6 values in the study of Rambod *et al*. and Aditia *et al*. was 9.9 pg/ml [11], [12].

Malnutrition inflammation score (MIS)

MIS was carried out according to the Kalantar-Zadeh method [10], [13], [14]. These were assessed by taking a medical history and physical and laboratory examinations. History taking included questions regarding changes in body weight, food intake, gastrointestinal symptoms, functional capacity, and comorbid diseases. The physical examination consisted of assessing subcutaneous fat and body mass index. The laboratory parameters included TIBC and albumin levels. Each component of MIS has four severity range: from 0 (normal) to 3 (very severe) [13], [14], [15].

Asymmetric dimethylarginine (ADMA) examination

An Agilent 1290 Infinity II LC System with 6460 Triple Quad MS (LC-MS/MS) was used for the chromatographic separation. ADMA was obtained from Merck (Darmstadt, Germany). ADMA values for a small risk of cardiovascular are <100 ng/mL (1.79 μmol/L) [16].

Data analysis

The data obtained were analyzed using SPPS version 22.0 (IBM, Armonk, NY, USA) testing the normality of the data using the Shapiro–Wilk. Analysis to determine the correlation between IL-6, MIS, and ADMA was using the Spearman test (with significantly $p < 0.05$).

Results

This study recruited a total of 30 patients, with 22 (72%) patients being male and 8 (28%) females (Figure 1).

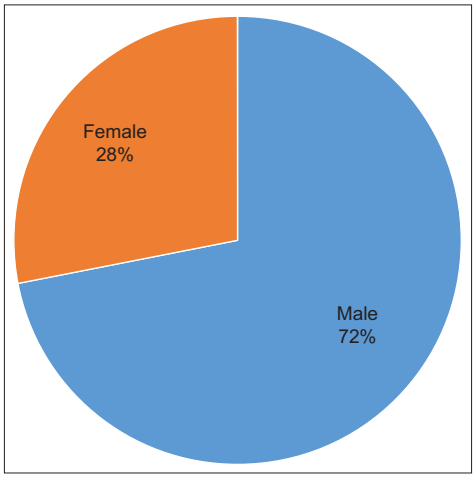

Figure 1: Participants distribution by sex

The median age was 56.5 (32−60) years. The length of hemodialysis in this group showed a median value of 3 (2−5) years. The median of IL-6 was 10.73 pg/ml (2.91−113.1 pg/ml). The overall median of ADMA was 104 ng/ml (71−168 ng/ml). Based on the malnutrition score, the median of MIS was 7 (2−9). The data are shown in Table 1.

Table 1: Characteristics of the participants

Characteristic	n	Minimum	Maximum	Median
Age (years)	30	32.00	60.00	56.50
HD duration (years)	30	2.00	5.00	3.00
BMI (kg/m^2)	30	16.51	29.76	22.15
Album (g/dL)	30	2.34	4.81	4.34
TIBC (mcg/dL)	30	128.00	388.00	224.50
ADMA (ng/mL)	30	71.00	168.00	104.00
IL-6 (pg/ml)	30	2.91	113.10	10.73
MIS	30	2.00	9.00	7.00

n: Number of research samples, BMI: Body mass index, TIBC: Total iron binding capacity, ADMA: Asymmetric dimethylarginine, IL-6: Interleukin 6, MIS: Malnutrition inflammation score, HD: Hemodialysis.

Correlation between IL-6 and ADMA

The Shapiro–Wilk normality test showed an abnormal data distribution. A Spearman correlation test was conducted to assess the correlation between IL-6 and ADMA. The result showed a significant relationship between IL-6 and ADMA (r = 0.440; p = 0.015). The correlation coefficient indicated that IL-6 have a moderate and unidirectional correlation with ADMA (Figure 2), in which the high IL-6 are also followed by high ADMA (Table 2).

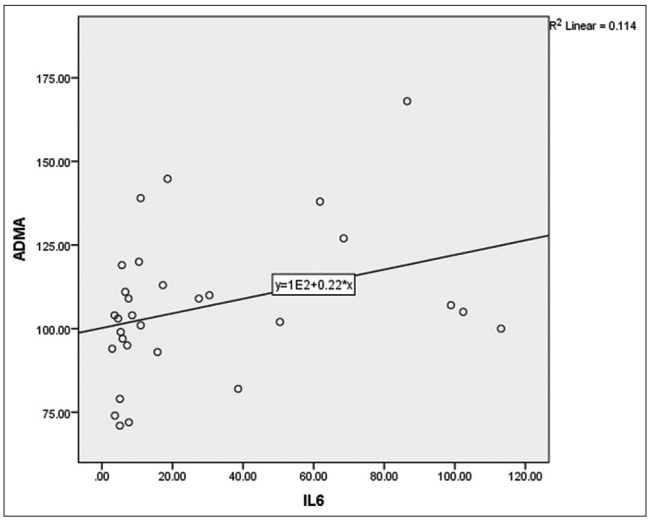

Figure 2: Graph of the correlation between IL-6 and ADMA

Correlation between MIS and ADMA

The Shapiro–Wilk normality test showed an abnormal data distribution; therefore, a Spearman correlation test was used to assess the correlation between MIS and ADMA. The result showed a significant correlation between MIS and ADMA (r = 0.378; p = 0.039). The correlation coefficient showed that MIS had a moderate and unidirectional level of correlation with ADMA (Figure 3), in which the high MIS is also followed by the high ADMA (Table 2).

Table 2: Correlation between variables

Correlation variable	n	r	p
IL-6 - ADMA	30	0.440	0.015
MIS - ADMA	30	0.378	0.039
IL-6 - MIS	30	0.682	0.000

n: Number of research samples, r: Correlation coefficient, ADMA: Asymmetric dimethylarginine, IL-6: Interleukin 6, MIS: Malnutrition inflammation score.

Correlation between IL-6 and MIS

The Shapiro–Wilk normality test showed an abnormal data distribution; therefore, a Spearman correlation test was used to assess the correlation between IL-6 levels and MIS. The result showed a significant correlation between IL-6 and MIS (r = 0.682; p = 0.0001). The correlation coefficient shows that the IL-6 as a moderate and unidirectional correlation with MIS (Figure 4), in which the high IL-6 was also followed by the high value of MIS (Table 2).

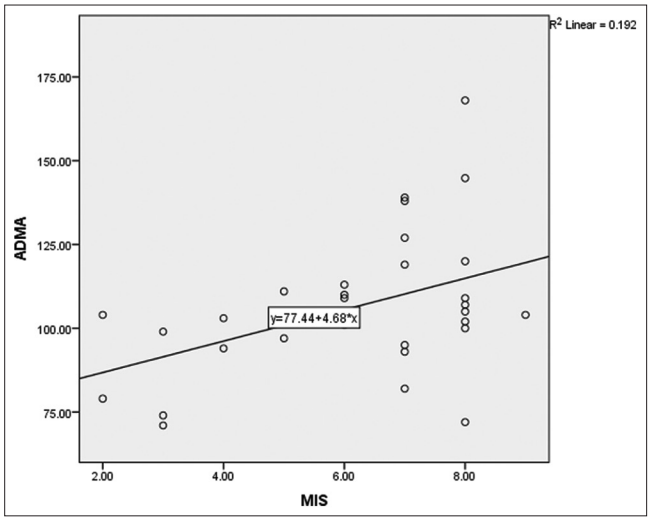

Figure 3: Graph of the Correlation between MIS and ADMA

Discussion

Our result showed a higher distribution of men compared to women (72%−28%), and the median age in this study was 56.5 years which was similar to data from the Indonesian Renal Registry in 2018 with the average age 45−54 years was 30.82%. These data showed that the prevalence of male patients undergoing hemodialysis was higher than female (57%−43%) [17]. A study by Permana *et al*. in Palembang in 2020 also found similar results, in which the number of male patients undergoing hemodialysis's was more than that of women (73% vs. 26.7%) [18].

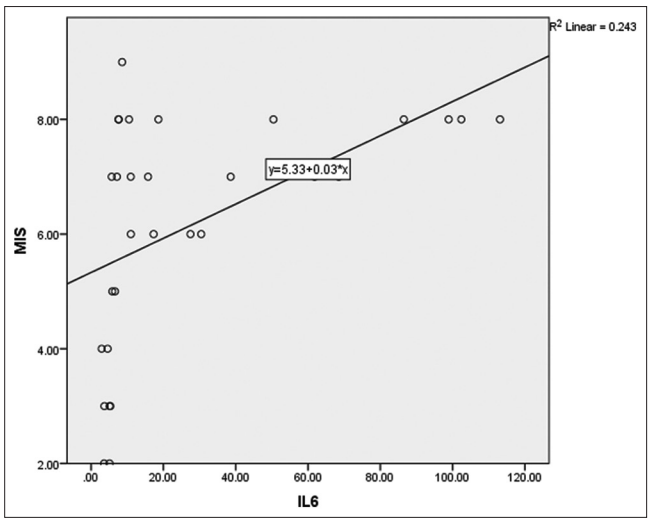

Figure 4: Graph of the Correlation between IL-6 and MIS

The average BMI in this study was 22.22 ± 3.29 kg/m^2. Similar results were found by Ho *et al*. in Taiwan in 2008 and Iyidogan *et al*. in Turkey in 2008, with the average BMI of 22.1 ± 3.5 kg/m^2 and 22.5 ± 0.7 kg/m^2, respectively [18], [19]. Differences in average BMI values can be caused by differences in body weight demographics, whereas obesity and overweight are often found in hemodialysis patients in western countries.

Interleukin-6 is one of the pro-inflammatory cytokines that initiates an acute phase response of hepatocyte cells and induces CRP production [20], [21]. The level of IL-6 in hemodialysis CKD patients was higher compared to the normal population and was associated with mortality rates, malnutrition, inflammation, and cardiovascular disease [21], [22]. The reference value of IL-6 used was <9.9 pg/mL [11], [12]. In this study, the average IL-6 was 28.05 ± 33.68 pg/ml, which was higher than normal values. This result was in accordance with a study by Kalantar-Zadeh *et al*. in Los Angeles in 2004, where the average of IL-6 in hemodialysis CKD patients was 22.6 ± 56.67 pg/ml [23]. Similar results were also reported by Kaizu *et al*. in Japan, Thiagarajan *et al*. and Herbelin *et al*. where the average of IL-6 was 11.7 ± 2.8 pg/ml, 16.12 ± 34.1 pg/ml, and 45.2 ± 3.9 pg/ml [18], [22], [23]. Elevated of IL-6 can be caused by hypertension, adipocytes, insulin resistance, excess fluid, persistent infections, and dialysis procedures such as using bio incompatible membranes, non-sterile dialysis techniques, and back filtration [24], [25]. Several studies have shown that IL-6 do not increase during the hemodialysis process but rather than increase in 2 h after completion of hemodialysis [18], [25]. The interaction of hemodialysis membranes and contaminated dialysis causes the release of endotoxins through high-flow dialysis membranes (High-flux), resulting in the activation of monocyte cells and release of IL-6 [20], [25]. The use of cellulose membranes more often leads to an increase in IL-6 compared to polysulfone membranes [26], [27], [28]. On the other hand, the uremic state can also cause an increase in IL-6, but routine hemodialysis also leads to a further increase of IL-6 [25], [29], [30]. Kaizu *et al*. found a positive association between elevated of IL-6 with the length of hemodialysis of >3 years, chronic disease conditions, uremic-related dialysis or oxidative stress conditions [20]. The average length of hemodialysis in our patients was 3.26 ± 1.14 years.

The MIS can represent all examinations to assess nutritional status and has been recognized by KDOQI as a panel for status protein-energy nutrition status [15]. This study showed that the average MIS in hemodialysis CKD patients was 6.17 ± 2.04, indicating a moderate malnutrition (MIS score 6−8). This results are similar to the study by Kalantar-Zadeh *et al*. on 83 hemodialysis CKD patients in San Fransico and 378 hemodialysis CKD patients in Los Angeles, with the average MIS of 8.3 ± 4.2 and 6.3 ± 3.9, respectively [10], [13]. A study by Visideo *et al*. also obtained an average result of MIS of 8.4 ± 3.5 [31]. Routine hemodialysis has a risk of malnutrition due to the catabolism effect of kidney replacement therapy, decreased appetite due to uremic conditions and nutritional restrictions that cause inadequate dietary intake, loss of nutrients through dialysis membranes, inflammation, and metabolic acidosis. These factors can cause hemodialysis CKD patients experience a malnutrition energy protein syndrome [31]. High MIS values are associated with poor nutritional status, high inflammation, mortality rate, and morbidity in hemodialysis CKD patients [11], [31], [32].

This study found that the median value of ADMA was 104.00 ng/ml (1.82 μmol/L), which was higher than the normal values. The results reported by Tripepi *et al*. in Italy in 2011 also found the median ADMA of 2.4 μmol/L [8]. Elevated ADMA can occur due to impaired renal excretion, such as in CKD or increased oxidative stress leading to decreased DDAH enzyme activity which is caused by older age, smoking, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia, and hypertension [33], [34], [35], [36]. Kielstein *et al*. also found that hemodialysis CKD patients with vascular atherosclerosis had higher of ADMA values than those without vascular complications [37].

Inflammation in CKD patients is multifactorial [26]. Hemodialysis-related and non- hemodialysis-related factors can cause inflammation by stimulating the synthesis of cytokines such as CRP, IFN-γ, IL-1, IL-6, and TNF-α [26]. Another biomarker related to inflammation is suPAR (soluble urokinase plasminogen activator receptor) [38]. High levels of suPAR and other pro-inflammatory mediators were associated with CKD progression [38], [39]. Pro-inflammatory cytokines that are also increased in prolonged proteinuria include transforming growth factor-ß (TGF-ß), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) [40].

In addition, it is well known that IL-6, TGF-ß, TNF- α, fibroblast growth factor-23 (FGF-23), VEGF, PDGF, and many more pro-inflammatory mediators which have a molecular weight between 20.000 and 45.000 Dalton can be removed by therapeutic plasma exchange (TPE). Dzulfikar Djalil Lh *et al*. found that TPE is effective in managing disease progression affected by IL-6 [41].

In this study, we found that most hemodialysis CKD patients had ADMA and IL-6 above normal values (66% and 66%). The study found a significant positive correlation between IL-6 and ADMA (r = 0.440, p = 0.015). A study conducted by Tripepi *et al*. on 225 hemodialysis CKD patients in Italy on 2011 found a significant positive correlation between IL-6 and ADMA (r = 0.18, p = 0.009) [8]. Cytokine IL-6 causes endothelial damage through eNOS and adiponectin expression. Recombinant injection of IL-6 worsens the incidence of atherosclerosis [27], [42]. Cytokine IL-6 stimulates ICAM-1, which can cause migration and adhesions of leukocytes passing through the endothelial surface; initiating the initial phase of fibrous plaque formation in the process of atherosclerosis; and an increase in IL-6 associated with the progressiveness of carotid atherosclerosis within 12 months of early dialysis therapy [25]. A study by Tripepi *et al*. found that ADMA was directly and significantly related to IL-6, thus signaling that both inflammatory processes and endothelial dysfunction occurred simultaneously in CKD patients [8].

A study conducted by Bolton *et al*. on 44 patients consisted of 23 CKD patients who underwent Hemodialysis and peritoneal dialysis, 16 CKD patients who had not undergone dialysis, 28 patients healthy as a control and 20 patients with stable angina. Bolton *et al*. found that IL-6 was significantly related to endothelial vasomotor functions (EDV) ($r = -0.43$, $p = 0.01$), vCAM-1 ($r = 0.45$, $p = 0.001$), ICAM-1 ($r = 0.38$, $p = 0.001$) in all groups, and IL-6 positively associated with ICAM-1 ($r = 0.72$, $p = 0.0001$) [43]. Boltom *et al*. revealed that an increase in IL-6 in CKD patients can predispose to the occurrence of vascular disease and sICAM-1 can be a marker of endothelial dysfunction [43].

A study conducted by Nawawi *et al*. on 74 patients who received atorvastatin therapy found an improvement in endothelial function through increased flow-mediated vasodilatation (FMD). It decreased levels of sICAM-1 and IL-6. Nawawi *et al*. revealed that IL-6 and sICAM-1 can be markers of endothelial dysfunction [44].

The results showed a significant positive correlation between MIS and ADMA ($r = 0.378$, $p = 0.039$). Several studies have found an association between inflammatory malnutrition syndrome with endothelial dysfunction in hemodialysis patients [45], [46]. Still, no one has yet found a correlation between MIS and ADMA in patients with hemodialysis. A study of inflammatory malnutrition related to endothelial dysfunction, first conducted by Demir *et al*. they found that there was a correlation between MIS with VCAM-1 ($r = 0.33$, $p = 0.004$) and FMD ($r = -0.35$, $p = 0.003$) as a parameters of endothelial dysfunction [47]. Melikian *et al*. studied endothelial function by examining ADMA and FMD in the brachial artery on 58 total samples. They found the ADMA, multiple regression model, to be the only independent factor of FMD ($p = 0.02$) [48]. A study by Juonala *et al*. consisting of 2090 adult patients showed that there was an inverse correlation between ADMA and brachial artery FMD, which was significant with a multivariate regression model based on age, sex, and cardiovascular risk factors, eGFR values and brachial artery diameter ($p = 0.01$) [49]. A study by Cupisti *et al*. on 38 patients undergoing routine hemodialysis showed that increased ADMA was associated with low BMI and albumin, both of which were markers of poor nutritional and inflammatory markers [50].

Increased inflammation and decreased antioxidants due to malnutrition can lead to endothelial dysfunction. Inflammatory cytokines causes an increase in oxidative stress, protein muscle degradation, synthesis of acute phases of reactants and endothelial cell damage [4], [9] suPAR which is expressed in endothelial type as well as podocyte and can be a marker of glomerular disease activity, systemic inflammation, and infection [39], [51].

Demir *et al*. found that the higher the MIS, the more severe the endothelial dysfunction [47]. A study by Kalantar-Zadeh *et al*. found a significant correlation between Subjective Global Assessment (SGA) and ADMA. When they compared MIS with SGA or Dialysis Malnutrition Score (DMS), it was considered that MIS is superior as an indicator malnutrition inflammation complex syndrome (MICS) [10].

This study found a significant positive correlation between IL-6 and MIS ($r = 0.682$, $p = 0.0001$). Thandavan *et al*. in India reported similar results in a correlation between IL-6 and MIS ($r = 0.304$, $p = 0.05$) [21]. The significant positive correlation between IL-6 and MIS values is the same as the study conducted by Rambod *et al*. in America, which found a positive correlation between IL-6 and MIS ($r = 0.26$, $p = 0.0001$) [9]. Similarly, Valencia *et al*. reported a study of 128 hemodialysis patients with in Mexico and found a positive correlation between IL-6 and MIS ($r = 0.327$, $p = 0.01$) [52].

Interleukin 6, as an inflammatory factor, plays a role in synthesizing acute-phase proteins that will inhibit albumin synthesis through regulating Messenger RNA (mRNA) albumin [5], [20], [53] High levels of IL-6 indicate a high inflammatory process that occurs, triggering inflammatory malnutrition syndrome in CKD patients with hemodialysis [54]. MIS is a combination of SGA scoring accompanied by BMI, serum albumin and transferrin components, consisting of ten components. A longitudinal study showed that MIS could be used as a good indicator for MICS in dialysis patients [11], [31]. Kaizu *et al*. suggested that IL-6 are significantly associated with malnutrition [20]. Several studies have revealed that MIS could describe the severity of inflammatory malnutrition syndrome in hemodialysis patients, where the higher the MIS, the more severe the degree of malnutrition and inflammation [13], [32], [47]. Rambod *et al*. revealed that when MIS is compared to other nutritional inflammatory markers, MIS is the suitable inflammatory marker and can replace IL-6 or CRP [11].

The limitation of this study was that the IL-6 examination was carried out on all CKD patients without distinguishing the membrane of the hemodialysis machine (conventional hemodialysis or hemodiafiltration). Further research is needed in the form of control case studies to compare IL-6, ADMA, and MIS in the control group and hemodialysis CKD patients.

Conclusion

There was a significant correlation between IL-6, MIS and ADMA. In addition, MIS, which is easily calculated, may serve as a practical tool to assess inflammatory malnutrition status and early prevention of malnutrition. Increasing IL-6 because of hemodialysis and non-hemodialysis procedure is associated with the progression of CKD, and it could be speculated to inhibit the production of IL-6 whether with TPE or using

biocompatible membrane (Polysulfon) and exchange of conventional to ultrapure dialysis fluid to reduce the levels of IL-6. In addition, using a high permeable membrane or hemofiltration and hemodiafiltration techniques, the use glucose-free dialysate, avoiding the reuse of dialyzers and intradialytic vitamin supplementation are alternative methods to improve nutritional status of CKD HD patient. Otherwise, anti-IL-6 monoclonal antibodies has been effective in rheumatoid patient as reducing the acute phase protein and therefore it is possible to do conduct more studies to determine the effect of anti-IL-6 monoclonal antibodies to improve the malnutrition related to inflammatory in CKD HD patient.

References

1. Luyckx VA, Stanifer JW, Tonelli M. The global burden of kidney disease and the sustainable development goals. Bull World Health Organ. 2018;96(6)414-22D. https://doi.org/10.2471/BLT.17.206441
   PMid:29904224
2. Hilmanto D, Mawardi F, Lestari AS, Widiasta A. Disease-associated systemic complications in childhood nephrotic syndrome: A systematic review. Int J Nephrol Renovasc Dis. 2022;15:53-62. https://doi.org/10.2147/IJNRD.S351053
   PMid:35241925
3. Widiasta A, Pardede SO, Rachmadi D. Correlation between LDL, HDL, total cholesterol, and triglyceride with the degree of chronic kidney disease in children. Am J Clin Med Res. 2017;5(1):1-5. https://doi.org/10.12691/ajcmr-5-1-1
4. As'Habi A, Tabibi H, Hedayati M, Mahdavi-Mazdeh M, Nozary-Heshmati B. Association of malnutrition-inflammation score, dialysis-malnutrition score and serum albumin with novel risk factors for cardiovascular diseases in hemodialysis patients. Ren Fail. 2015;37(1):113-6. https://doi.org/10.3109/0886022X.2014.967615
   PMid:25296104
5. Stenvinkel P, Barany P, Heimbu̇rger O, Pecoits-Filho R, Lindholm B. Mortality, malnutrition, and atherosclerosis in ESRD: What is the role of interleukin-6? Kidney Int Suppl. 2002;61(80):103-8. https://doi.org/10.1046/j.1523-1755.61.s80.19.x
   PMid:11982823
6. Rao P, Reddy GC, Kanagasabapathy AS. Malnutrition-inflammation-atherosclerosis syndrome in chronic kidney disease. Indian J Clin Biochem. 2008;23(3):209-17. https://doi.org/10.1007/s12291-008-0048-9
   PMid:23105756
7. Roumeliotis S, Mallamaci F, Zoccali C. Endothelial dysfunction in chronic kidney disease, from biology to clinical outcomes: A 2020 update. J Clin Med. 2020;9(8):2359. https://doi.org/10.3390/jcm9082359
8. Tripepi G, Raso FM, Sijbrands E, Seck MS, Maas R, Boger R, *et al*. Inflammation and asymmetric dimethylarginine for predicting death and cardiovascular events in ESRD patients. Clin J Am Soc Nephrol. 2011;6(7):1714-21. https://doi.org/10.2215/CJN.11291210
   PMid:21642364
9. Didion SP. Cellular and oxidative mechanisms associated with interleukin-6 signaling in the vasculature. Int J Mol Sci. 2017;18(12):2563. https://doi.org/10.3390/ijms18122563
   PMid:29186034
10. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2001;38(6):1251-63. https://doi.org/10.1053/ajkd.2001.29222
    PMid:11728958
11. Rambod M, Bross R, Zitterkoph J, Benner D, Pithia J, Colman S, *et al*. Association of malnutrition-inflammation score with quality of life and mortality in maintenance hemodialysis patients: A 5--year prospective cohort study. Am J Kidney Dis. 2008;53(2):289-309. https://doi.org/10.1053/j.ajkd.2008.09.018
    PMid:19070949
12. Aditia K, Palar S, Karema-Kaparang AM, Moeis ES, Sugeng C, Umboh O. POS-552 correlation of interleukin-6 levels, high sensitivity c-reactive protein, and malnutrition inflammation score with quality of life chronic kidney disease patients undergoing routine hemodialysis. Kidney Int Rep. 2022;7(2):S239. https://doi.org/10.1016/j.ekir.2022.01.584
13. Lopes AA. The malnutrition-inflammation score: A valid nutritional tool to assess mortality risk in kidney transplant patients. Am J Kidney Dis. 2011;58(1):7-9. https://doi.org/10.1053/j.ajkd.2011.04.003
    PMid:21684436
14. González-Ortiz AJ, Arce-Santander CV, Vega-Vega O, Correa-Rotter R, Espinosa-Cuevas MD. Assessment of the reliability and consistency of the "malnutrition inflammation score" (MIS) in Mexican adults with chronic kidney disease for diagnosis of protein-energy wasting syndrome (PEW). Nutr Hosp. 2014;31(3):1352-8. https://doi.org/10.3305/nh.2015.31.3.8173
    PMid:25726233
15. Aggarwal HK, Jain D, Chauda R, Bhatia S, Sehgal R. Assessment of malnutrition inflammation score in different stages of chronic kidney disease. Pril (Makedon Akad Nauk Umet Odd Med Nauki. 2018;39(2-3):51-61. https://doi.org/10.2478/prilozi-2018-0042
    PMid:30864357
16. ADMA/SDMA. United States of America: Cleveland HeartLab, Inc.; 2015. Available from: https://www.clevelandheartlab.com/tests/adma-sdma [Last accessed on 2022 Jan 02].
17. Indonesian Renal Registry. 11th Report of Indonesian Renal Registry. Perkumpulan Nefrologi Indonesia, Indones. Ren. Regist. (2018) 1-46
18. Ho L, Wang HH, Peng YS, Chiang CK, Huang JW, Hung KY, *et al*. Clinical utility of malnutrition-inflammation score in maintenance hemodialysis patients: Focus on identifying the best cut-off point. Am J Nephrol. 2008;28(5):840-6. https://doi.org/10.1159/000137684
    PMid:18535370
19. Oner-Iyidogan Y, Oner P, Kocak H, Gurdol F, Bekpinar S, Unlucerci Y, *et al*. Dimethylarginines and inflammation markers in patients with chronic kidney disease undergoing dialysis. Clin Exp Med. 2009;9:235-41. https://doi.org/10.1007/s10238-009-0035-3
    PMid:19238516
20. Kaizu Y, Kimura M, Yoneyama T, Miyaji K, Hibi I, Kumagai H. Interleukin-6 may mediate malnutrition in chronic hemodialysis patients. Am J Kidney Dis. 1998;31(1):93-100. https://doi.org/10.1053/ajkd.1998.v31.pm9428458
    PMid:9428458
21. Kato A, Odamaki M, Takita T, Maruyama Y, Kumagai H, Hishida A. Association between interleukin-6 and carotid atherosclerosis in hemodialysis patients. Kidney Int. 2002;61(3):1143-52. https://doi.org/10.1046/j.1523-1755.2002.00215.x

PMid:11849469

22. Muzasti RA, Hariman H, Daulay ER. Interleukin 6 concentration elevation as a risk of carotid intimamedia thickness in chronic kidney disease patients with dialysis. Med Glas (Zenica). 2020;17(2):346-51. https://doi.org/10.17392/1172-20
PMid:32662610
23. Kalantar-Zadeh K, Kopple JD, Humphreys MH, Block G. Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. Nephrol Dial Transplant. 2004;19(6):1507-19. https://doi.org/10.1093/ndt/gfh143
PMid:15069177
24. Thandavan T, Abraham G, Soundararajan P, Chandrasekaran V. Interleukin 6 strongly correlates with malnutrition inflammation score and it is strong predictor for mortality in hemodialysis patients. Urol Nephrol Open Access J. 2015;2(2):40-2. https://doi.org/10.15406/unoaj.2015.02.00030
25. Herbelin A, Ureña P, Nguyen AT, Zingraff J, Descamps-Latscha B. Elevated circulating levels of interleukin-6 in patients with chronic renal failure. Kidney Int. 1991;39(5):954-60. https://doi.org/10.1038/ki.1991.120
PMid:2067212
26. Jofré R, Rodriguez-Benitez P, López-Gómez JM, Pérez-Garcia R. Inflammatory syndrome in patients on hemodialysis. J Am Soc Nephrol. 2006;17(12 Suppl 3):S274-80. https://doi.org/10.1681/ASN.2006080926
PMid:17130274
27. Pecoits-Filho R, Lindholm B, Axelsson J, Stenvinkel P. Update on interleukin-6 and its role in chronic renal failure. Nephrol Dial Transplant. 2003;18(6):1042-5. https://doi.org/10.1093/ndt/gfg111
PMid:12748331
28. Małgorzewicz S, Heleniak Z, Lichodziejewska-Niemierko M, Rutkowski R, Aleksandrowicz-Wrona E, Dębska-Ślizień A. Protein-energy wasting and asymmetric dimethylarginine in peritoneal dialysis patients. Acta Biochim Pol. 2018;65(4):581-4. https://doi.org/10.18388/abp.2018_2634
PMid:30508418
29. Nakahama H, Tanaka Y, Shirai D, Miyazaki M, Imai N, Yokokawa T, *et al*. Plasma interleukin-6 levels in continuous ambulatory peritoneal dialysis and hemodialysis patients. Nephron. 1992;61(2):132-4. https://doi.org/10.1159/000186859
PMid:1630534
30. Cavaillon JM, Poignet JL, Fitting C, Delons S. Serum interleukin-6 in long-term hemodialyzed patients. Nephron. 1992;60(3):307-13. https://doi.org/10.1159/000186770
PMid:1565183
31. Visiedo L, Rey L, Rivas F, López F, Tortajada B, Giménez R, *et al*. The impact of nutritional status on health-related quality of life in hemodialysis patients. Sci Rep. 2022;12(1):3029. https://doi.org/10.1038/s41598-022-07055-0
PMid:35194119
32. Sohrabi Z, Eftekhari MH, Eskandari MH, Rezaeianzadeh A, Sagheb MM. Malnutrition-inflammation score and quality of life in hemodialysis patients: Is there any correlation? Nephrourol Mon. 2015;7(3):e27445. https://doi.org/10.5812/numonthly.7(3)2015.27445
PMid:26034747
33. Aldámiz-Echevarría L, Andrade F. Asymmetric dimethylarginine, endothelial dysfunction and renal disease. Int J Mol Sci. 2012;13(9):11288-311. https://doi.org/10.3390/ijms130911288
PMid:23109853
34. Oliva-Damaso E, Oliva-Damaso N, Rodriguez-Esparragon F, Payan J, Baamonde-Laborda E, Gonzalez-Cabrera F, *et al*. Asymmetric (ADMA) and symmetric (SDMA) dimethylarginines in chronic kidney disease: A clinical approach. Int J Mol Sci. 2019;20:(15):3668. https://doi.org/10.3390/ijms20153668
PMid:31357472
35. Schulze F, Lenzen H, Hanefeld C, Bartling A, Osterziel KJ, Goudeva L, *et al*. Asymmetric dimethylarginine is an independent risk factor for coronary heart disease: Results from the multicenter coronary artery risk determination investigating the influence of ADMA concentration (CARDIAC) study. Am Heart J. 2006;152(3):493. https://doi.org/10.1016/j.ahj.2006.06.005
PMid:16923419
36. Kocaman SA. Asymmetric dimethylarginine, NO and collateral growth. Anadolu Kardiyol Derg. 2009;9(5):417-20.
PMid:19819795
37. Kielstein JT, Böger RH, Bode-Böger SM, Schäffer J, Barbey M, Koch KM, *et al*. Asymmetric dimethylarginine plasma concentrations differ in patients with end-stage renal disease: Relationship to treatment method and atherosclerotic disease. J Am Soc Nephrol. 1999;10(3):594-600. https://doi.org/10.1681/ASN.V103594
PMid:10073610
38. Wang Y, Gao L. Inflammation and cardiovascular disease associated with hemodialysis for end-stage renal disease. Front Pharmacol. 2022;13:800950. https://doi.org/10.3389/fphar.2022.800950
PMid:35222026
39. Widiasta A, Wahyudi K, Nugrahapraja H, Sribudiani Y, Rachmadi D. The unique difference between serum level of soluble urokinase plasminogen activator receptor (suPAR) in steroid-resistant nephrotic syndrome children treated with an alkylating agent and calcineurin inhibitors. J Compr Pediatr. 2021;12(2): e109912. https://doi.org/10.5812/compreped.109912
40. Rachmadi D, Widiasta A, Pusparani C, Wahyudi K, Nugrahapraja H, Sribudiani Y. Higher baseline integrin beta-1 level associated with possible increase in the remission of steroid-resistant nephrotic syndrome using cyclophosphamide treatment. Int J Pharm Res. 2021;13(2):4223-32. https://doi.org/10.31838/ijpr/2021.13.02.517
41. Lh DD, Widiasta A, Ghrahani R, Hilmanto D, Rachmadi D. Therapeutic plasma exchange as a promising therapeutic modality in the management of acute cytokine storms and secondary prevention of chronic kidney disease in children during pandemic. Int J Pharm Res. 2021;13(2):4473-86. https://10.31838/ijpr/2021.13.02.259
42. Su H, Lei CT, Zhang C. Interleukin-6 signaling pathway and its role in kidney disease: An update. Front Immunol. 2017;8:405. https://doi.org/10.3389/fimmu.2017.00405
PMid:28484449
43. Bolton CH, Downs LG, Victory JG, Dwight JF, Tomson CR, Mackness MI, *et al*. Endothelial dysfunction in chronic renal failure: Roles of lipoprotein oxidation and pro-inflammatory cytokines. Nephrol Dial Transplant. 2001;16(6):1189-97. https://doi.org/10.1093/ndt/16.6.1189
PMid:11390719
44. Nawawi H, Osman NS, Annuar R, Khalid BA, Yusoff K. Soluble intercellular adhesion molecule-1 and interleukin-6 levels reflect endothelial dysfunction in patients with primary hypercholesterolaemia treated with atorvastatin. Atherosclerosis. 2003;169(2):283-91. https://doi.org/10.1016/S0021-9150(03)00193-X
PMid:12921980
45. Aguilera A, Sánchez-Tomero JA, Bajo MA, Ruiz-Caravaca ML, Alvarez V, del Peso G, *et al*. Malnutrition-inflammation syndrome is associated with endothelial dysfunction in peritoneal dialysis patients. Adv Perit Dial. 2003;19:240-5.
PMid:14763071

46. Stenvinkel P, Chung SH, Heimbürger O, Lindholm B. Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. Perit Dial Int. 2001;21 Suppl 3:S157-62. https://doi.org/10.1177/089686080102103S27
PMid:11887812

47. Demir M, Kucuk A, Sezer MT, Altuntas A, Kaya S. Malnutrition-inflammation score and endothelial dysfunction in hemodialysis patients. J Ren Nutr. 2010;20(6):377-83. https://doi.org/10.1053/j.jrn.2010.03.002
PMid:20663689

48. Melikian N, Wheatcroft SB, Ogah OS, Murphy C, Chowienczyk PJ, Wierzbicki AS, *et al*. Asymmetric dimethylarginine and reduced nitric oxide bioavailability in young black African men. Hypertension. 2007;49(4):873-7. https://doi.org/10.1161/01.HYP.0000258405.25330.80
PMid:17261643

49. Juonala M, Viikari JS, Alfthan G, Marniemi J, Kähönen M, Taittonen L, *et al*. Brachial artery flow-mediated dilation and asymmetrical dimethylarginine in the cardiovascular risk in young Finns study. Circulation. 2007;116(12):1367-73. https://doi.org/10.1161/CIRCULATIONAHA.107.690016
PMid:17724260

50. Cupisti A, Saba A, D'Alessandro C, Meola M, Panicucci E, Panichi V, *et al*. Dimethylarginine levels and nutritional status in hemodialysis patients. J Nephrol. 2009;22(5):623-9.
PMid:19809995

51. Backes Y, van der Sluijs KF, Mackie DP, Tacke F, Koch A, Tenhunen JJ, *et al*. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: A systematic review. Intensive Care Med. 2012;38(9):1418-28. https://doi:10.1007/s00134-012-2613-1
PMid:22706919

52. Valencia VC, Rodríguez OM, Sandoval ME, Bermúdez JA, Castellanos SG, de la Cruz CO, *et al*. Prevalence of malnutrition-inflammation complex syndrome and its correlation with thyroid hormones in chronic haemodialysis patients. Nefrologia (Engl Ed). 2018;38(1):57-63. https://doi.org/10.1016/j.nefroe.2017.11.019
PMid:29102271

53. Kaysen GA, Rathore V, Shearer GC, Depner TA. Mechanisms of hypoalbuminemia in hemodialysis patients. Kidney Int. 1995;48(2):510-6. https://doi.org/10.1038/ki.1995.321
PMid:7564120

54. Schepers E, Barreto DV, Liabeuf S, Glorieux G, Eloot S, Barreto FC, *et al*. Symmetric dimethylarginine as a proinflammatory agent in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(10):2374-83. https://doi.org/10.2215/CJN.01720211
PMid:21817129