RESEARCH ARTICLE

Could Complete Blood Count Parameters and Non-fasting Cholesterol Profile Describe Inflammation and Oxidative Stress in Chronic Kidney Disease?

Ika Nindya Kadariswantiningsih[1], Mochammad Thaha[2,*], Cahyo Wibisono Nugroho[2], Berliana Hamidah[3], Haerani Rasyid[4], Zaky El Hakim[5], Maulana Muhtadin Suryansyah[5], Mohammad Yusuf Alsagaff[6], Djoko Santoso[1], Maulana Antiyan Empitu[7] , Yusuke Suzuki[8]

[1]Department of Medical Microbiology, Faculty of Medicine, Airlangga University, Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Airlangga University, Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya, Indonesia
[3]Department of Medical Biology, Faculty of Medicine, Airlangga University, Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya, Indonesia
[4]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Jl. Perintis Kemerdekaan Km. 10, Makassar, Indonesia
[5]Medical Science Program, Faculty of Medicine, Airlangga University, Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya, Indonesia
[6]Department of Cardiology, Faculty of Medicine, Airlangga University, Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya, Indonesia
[7]Department of Pharmacology, Faculty of Medicine, Airlangga University, Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya, Indonesia
[8]Division of Nephrology, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, Japan

*Corresponding author. E-mail: mochthaha@yahoo.com

Received date: Oct 20, 2017; Revised date: Jul 18, 2018; Accepted date: Aug 3, 2018

Abstract

BACKGROUND: Establishment of inexpensive clinical laboratory tests to evaluate inflammation and oxidative stress is urgently needed in the limited resources settings. This study aims to investigate the potential of complete blood count (CBC) parameters and non-fasting cholesterol profile parameters to describe inflammation and oxidative stress in chronic kidney disease (CKD) patients.

METHODS: Measurement of CBC, non-fasting cholesterol profile, high sensitivity C-reactive protein (hs-CRP) and malondialdehyde (MDA) were performed in 71 CKD patients grouped into hemodialysis (HD) and non-hemodialysis (non-HD). Correlation analysis were performed to assess the potential of CBC and cholesterol profile to describe the level of hs-CRP and MDA.

RESULTS: In the HD group, total cholesterol was moderately associated with hs-CRP while total cholesterol/HDL-C ratio, monocyte/HDL-C ratio, monocyte/LDL-C ratio, neutrophil/HDL-C ratio, neutrophil/LDL-C ratio, platelet/HDL-C ratio and platelet/LDL-C ratio were strongly associated with hs-CRP. In the non-HD group, only neutrophil/total cholesterol ratio and platelet/total cholesterol ratio that were associated with hs-CRP. Total cholesterol, monocyte/LDL-C ratio, neutrophil/LDL-C ratio and platelet/LDL-C ratio were moderately associated with MDA while total cholesterol/HDL-C ratio, monocyte/HDL-C ratio, neutrophil/HDL-C ratio and platelet/HDL-C ratio were strongly associated respectively with MDA in HD group. In the non-HD group, total cholesterol/HDL-C ratio, neutrophil/HDL-C ratio and platelet/HDL-C ratio were moderately associated with MDA in non-HD group while monocyte/HDL-C ratio was weakly associated with MDA.

CONCLUSION: Some CBC parameters and non-fasting cholesterol profile such as cholesterol/HDL-C, monocyte/HDL-C, neutrophil/HDL-C and platelet/HDL-C ratio were strongly associated with the level of hs-CRP and MDA. Further study with higher number of subjects is needed to assess whether this parameter represent prognostic value among CKD patients.

KEYWORDS: inflammation, oxidative stress, CRP, MDA, TAC, 8-OHdG, CBC, cholesterol

Indones Biomed J. 2018; 10(3): 270-7

Introduction

Cardiovascular disease (CVD) is the major contributor of mortality in chronic kidney disease (CKD).(1) Mortality due to CVD in CKD patients is 10- to 20-fold higher compare to general population.(1) Continuous assessment of CVD risk factor is helpful to guide modification of therapy to prevent CVD in CKD patients.

Inflammation and oxidative stress appear to increase as CKD progresses and play pivotal roles in the pathogenesis and progression of CKD.(2) These two factors are regarded as non-traditional risk factors that highly contributed to the development of CVD in patients with CKD.(2) Inflammation and oxidative stress are also associated with higher mortality in patients receiving long-term hemodialysis therapy.(3) Therefore, continuous assessment of inflammation and oxidative stress will be useful to predict CVD risk in the CKD patients.

High sensitivity C-reactive protein (hs-CRP) is one of the most widespread inflammatory biomarkers commonly used for clinical purposes since it has several advantages such as good chemical stability and long half-life without diurnal variation.(4) Malondialdehyde (MDA), a marker of lipid oxidation on erythrocyte surface, is a biomarker to assess oxidative stress in CKD patients.(5) The hs-CRP and MDA are commonly used in developed countries to evaluate inflammation and oxidative stress.(5) However, in the developing countries, continuous evaluation of inflammation and oxidative stress of CKD patients through hs-CRP and MDA is still difficult.(6) Unfortunately, there are no established routine affordable clinical laboratory tests that could be used to evaluate inflammation and oxidative stress in CKD patients.

Previous studies showed that ratio of neutrophil to lymphocytes, two parameters in the complete blood count (CBC) test, could be used to predict inflammation in several diseases.(7,8) Refunctioning routine laboratory test to evaluate inflammation and oxidative stress will help health provider in health center with limited facilities to perform uninterrupted continuous assessments of CVD risk in CKD patients in a more feasible way. CBC test and non-fasting cholesterol profile were two kinds of routine laboratory test that could be perform in almost all health center with relatively affordable cost. In addition, these tests could be done in patients without any preparations such as 10 hours of fasting. So, these kind of clinical laboratory tests could be performed in CKD patients with small limitations. Therefore, this study aims to investigate the associations between hs-CRP and MDA as established biomarkers of inflammation and oxidative stress with CBC and non-fasting cholesterol profile that are routinely tested in CKD patients.

Methods

Study Design and Population Selection

Participants for this cross-sectional study were recruited consecutively from outpatient clinics and hemodialysis units of government and private hospitals in Surabaya and Makassar, Indonesia, from March until August 2017. The number of samples required for this study was calculated based on α of 0.05, β of 0.2 and expected correlation coefficient (r) of 0.5 for non-hemodialysis (non-HD) group and r of 0.6 for hemodialysis (HD) group.(9) The expected correlation coefficient was calculated based on previous study.(7,8,10) For this study, a total of 71 patients that $\geq$ 21-year-old with diagnosis of CKD were recruited. The diagnosis of CKD was confirmed by The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K-DOQI) criteria based on CKD epidemiology collaboration (CKD-EPI) equation (estimated glomerular filtration rate (eGFR) $\leq$ 60 mL/min/1,73m^2; urine albumin, albumin to creatinine ratio).(11) Exclusion criteria included overt infection, fever in the last 3 days, signs of infection, acute inflammatory disease, and malignancy. The study protocol was approved by Ethics Committee of Universitas Airlangga hospital Surabaya, Indonesia (Reference No. 093/IGH/2017).

Study participants underwent a detailed review of their disease history, physical examinations, and laboratory measurements at the time of enrollment. Subjects were classified based on their hemodialysis status. Subjects who received routine hemodialysis treatment were belong to HD group, while subjects who did not received any hemodialysis treatment were belong to non-HD group. Since we expected a higher correlation coefficient in the HD group, the number of required samples in the HD group was fewer than in the non-HD group.

Laboratory Measurements

Participants underwent blood and urine sampling early in the morning. Serum creatinine, serum cystatin-C and hemoglobin A1c (HbA1c) were measured based on established laboratory method previously explained.(12)

CBC and non-fasting cholesterol profile (total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C)) were measured from blood sample of the patients based on established laboratory method previously explained (REF). The hs-CRP was used as an inflammatory biomarker. hs-CRP was measured in blood using particle enhanced turbidimetry (Rohce Diagnostic, CA, USA). MDA was used as biomarker of oxidative stress. MDA was measured in the blood serum process by high-performance liquid chromatography (HPLC) method using Agilent 1100. All of the laboratory measurements were done in the good laboratory practice certified laboratory.

Statistical Analysis

The quantitative data was analyzed using Saphiro-Wilk for normality test. For normally distributed variables, data were shown as mean±SD. For skewed variables, data were shown as median and interquartile range (1st quartile - 3rd quartile). To investigate the differences between f two groups, Student's T-test was used if data had normal distribution and Mann-Whitney U-test was used in case of data with non-normal distribution. Chi-square test was used to evaluate the difference between categorical data of two group. Correlation between variables was performed using Pearson correlation test. All tests were two-tailed with significance level of 0.05. The statistical analyses were performed using XLSTAT software version 2016.02.28451.

Results

Characteristics of the Study Participants

Characteristics of the study participants based on hemodialysis status were shown in the Table 1. As expected, kidney function parameters were significantly better in No-HD than in HD group ($p<0.0001$ for eGFR, urine ACR, serum creatinine, and serum cystatin-C), while the number of erythrocytes ($p=0.006$) was significantly lower in the HD than in non-HD group. Regarding to the CVD risk factors, HD group showed more CVD risk factors compare to non-HD since it had significantly higher blood pressure both systolic blood pressure ($p<0.0001$) and diastolic blood pressure ($p=0.016$), higher inflammation as shown by higher level of hs-CRP ($p=0.010$) and also higher level of oxidative stress as shown by higher level of serum MDA ($p<0.0001$). However, cholesterol profile of HD group showed significantly lower level of total cholesterol ($p=0.013$) and LDL-C (p=0.037) compare to non-HD.

Combination of Blood Count Parameters and Non-fasting Cholesterol Profiles are Highly Associated with hs-CRP

In order to investigate the relationship between CBC parameters, cholesterol profile, and hs-CRP as an established marker of inflammation, we performed correlation tests between each single or combination of CBC parameters with hs-CRP. However, there is no single CBC parameters or combination CBC parameters that was associated with hs-CRP (data not shown).

Then, we performed correlation tests between each single parameters or combination of cholesterol profile parameters with hs-CRP. Total cholesterol ($p=0.008$, r=0.547) and total cholesterol/HDL-C ratio ($p<0.0001$, r=0.733) were moderately and strongly associated respectively with hs-CRP in the HD group as shown in the Table 2.

Next, we performed correlation tests between combination of CBC parameters and cholesterol profile parameters with hs-CRP. In HD group, combination between monocyte or neutrophil or platelet and HDL-C or LDL-C (monocyte/HDL-C ratio ($p<0.0001$, r=0.776), monocyte/LDL-C ratio ($p<0.0001$, r=0.798), neutrophil/HDL-C ratio ($p<0.0001$, r=0.757), neutrophil/LDL-C ratio ($p<0.0001$, r=0.771), platelet/HDL-C ratio ($p<0.0001$, r=0.761) and platelet/LDL-C ratio ($p<0.0001$, r=0.801)) were strongly associated with hs-CRP while in the non-HD, only neutrophil/total cholesterol ratio ($p=0.006$, r=0.404) and platelet/total cholesterol ratio ($p=0.008$, r=0.392) that were associated with hs-CRP.

Combination of CBC Parameters and Non-fasting Cholesterol Profiles are Highly Associated with Serum MDA

To evaluate the relationship between complete blood count parameters, cholesterol profile, and serum MDA, as an established marker of oxidative stress, we performed correlation tests between each single or combination of CBC parameters with MDA. However, there is no single CBC parameters or combination CBC parameters that was associated with MDA (data not shown).

Then, we performed correlation tests between each single parameters or combination of cholesterol profile parameters with MDA. Total cholesterol ($p<0.0001$, r=0.690) and total cholesterol/HDL-C ratio ($p<0.0001$, r=0.784) were moderately and strongly associated respectively with MDA in HD group as shown in the Table 3. Total cholesterol/HDL-C ratio ($p<0.0001$, r=0.570) was also moderately associated with MDA in non-HD group.

Table 1. Characteristics of the dialysis and pre-dialysis subjects.

Characteristics	CKD HD (n=26)	CKD Non-HD (n=45)	*p*- value
Age (years)$^{+}$	57.62 ± 10.98	58.13 ± 5.92	NS
Sex (Female/Male)	12/14	18/27	NS
Kidney Function			
eGFR (mL/minute/1.73 m^2)	3 (2-4)	29 (22-60)	0.000*
Urine ACR (mg/g)	1789 (834-3473)	184 (18-803)	0.000*
Serum Creatinine (mg/dL)	14.14 (11.51-15.95)	1.88 (1.29-2.59)	0.000*
Serum Cystatin-C (mg/L)	7.42 (6.58-7.94)	1.88 (1.28-2.61)	0.000*
Complete Blood Count			
Leukocytes (10^9/L)	7.95 (6.50-9.45)	7.80 (7.00-9.90)	NS
Neutrophil (10^9/L)	5.10 (4.01-6.74)	4.80 (4.19-5.82)	NS
Lymphocytes (10^9/L)	1.48 (1.16-1.62)	1.85 (1.56-2.39)	0.000*
Eosinophil (10^9/L)	0.33 (0.24-0.47)	0.23 (0.16-0.41)	0.034*
Basophil (10^9/L)	0.050 (0.03-0.07)	0.051 (0.03-0.06)	NS
Monocytes (10^9/L)	0.47 (0.36-0.59)	0.49 (0.35-0.54)	NS
Erythrocytes ($10^6/cm^3$)$^{+}$	3.90 ± 0.49	4.34 ± 0.69	0.006*
Hemoglobin (g/dL)	11.41 ± 1.48	12.10 ± 1.77	NS
Platelets ($10^3/mm^3$)$^{+}$	233.23 ± 59.61	248.13 ± 73.08	0.004*
Hematocrit (%)	35.94 ± 4.60	37.28 ± 5.41	NS
CVD Risk Factor measurements			
HbA1c (%)	6.15 (5.52-6.85)	6.90 (6.00-8.30)	0.028*
Systolic Blood Pressure (mmHg)	156 (143-167)	126 (112-132)	0.000*
Diastolic Blood Pressure (mmHg)$^{+}$	82 ± 9	75 ± 13	0.016*
Total Cholesterol (mg/dL)	189 (151-206)	215 (182-245)	0.013*
HDL Cholesterol (mg/dL)$^{+}$	39 ± 13	44 ± 15	NS
LDL Cholesterol (mg/dL)	107 (83-126)	130 (101-155)	0.037*
hs-CRP	2.10 (1.65-8.05)	1.40 (0.90-3.20)	0.010*
Serum MDA (mmol/L)	3.15 (2.82-3.69)	2.37 (2.16-2.67)	0.000*

Data are expressed in Mean ± SD^{+} or Median (Interquartile range). eGFR: estimated glomerular filtration rate; ACR: Albumin to creatinine ratio; HbA1c: Hemoglobin A1c; hs-CRP: High sensitivity C-reactive protein; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; MDA: Malondialdehyde; NS: Not significant. *p<0.05 was considered significant.

Next, we performed correlation tests between combination of CBC parameters and cholesterol profile parameters with CRP. In HD group, combination between monocyte or neutrophil or platelet and HDL-C (monocyte/HDL-C ratio (p<0.0001, r=0.766), neutrophil/HDL-C ratio (p<0.0001, r=0.753) and platelet/HDL-C ratio (p<0.0001, r=0.766) were strongly associated with MDA while combination between monocyte or neutrophil or platelet and LDL-C (monocyte/LDL-C ratio (p=0.003, r=0.606), neutrophil/LDL-C ratio (p=0.005, r=0.578) and platelet/LDL-C ratio (p=0.001, r=0.655) were moderately associated with MDA. In non-HD group, combination between monocyte or neutrophil or platelet and HDL-C (monocyte/HDL-C ratio (p=0.002, r=0.459), neutrophil/HDL-C ratio (p<0.0001, r=0.532) and platelet/HDL-C ratio (p<0.0001, r=0.594) were associated with MDA.

Discussion

CVD is the leading cause of mortality in CKD.(2) Inflammation and oxidative stress are regarded as non-traditional risk factors that highly contributed to the development of CVD in patients with CKD.(13,14)

Table 2. Correlation between combination of blood counts and cholesterol profile with CRP among subjects of HD and non-HD group.

Variable	hs-CRP			
	HD		Non-HD	
	r	*p*- value	r	*p*- value
Total cholesterol	0.547	0.008*	-0.036	0.812
Total cholesterol/HDL-C	0.733	0.000*	0.05	0.746
Monocyte/HDL-C	0.776	0.000*	0.278	0.064
Monocyte/LDL-C	0.798	0.000*	0.191	0.208
Monocyte/Total cholesterol	0.176	0.434	0.213	0.160
Neutrophil/HDL-C	0.757	0.000*	0.247	0.101
Neutrophil/LDL-C	0.771	0.000*	0.254	0.092
Neutrophil/Total cholesterol	0.205	0.360	0.404	0.006*
Platelet/HDL-C	0.761	0.000*	0.154	0.314
Platelet/LDL-C	0.801	0.000*	0.223	0.141
Platelet/Total cholesterol	0.208	0.353	0.392	0.008*

HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol. *p<0.05 was considered significant.

Continuous assessment of inflammation and oxidative stress through hs-CRP and MDA is useful to predict CVD risk in the CKD patients.(14,15) Unfortunately, assessment of these two commonly used biomarkers for inflammation and oxidative stress in developed countries is infeasible in most developing countries with limited resources and facilities. (6) Establishment of inexpensive clinical laboratory tests that could be used to evaluate inflammation and oxidative stress is urgently needed in the area with limited resources and facilities.

Several studies showed the potential of using routine laboratory tests to become surrogate marker for inflammation in wide range of diseases, including CKD.(7,8,10) Previous study recommended neutrophil/lymphocyte ratio (NLR)

Table 3. Correlation between combination of blood counts and cholesterol profile with serum MDA among subjects of HD and non-HD group.

Variable	Serum MDA			
	HD		Non-HD	
	r	*p*- value	r	*p*- value
Total cholesterol	0.69	0.000*	313	0.036*
Total cholesterol/HDL-C	0.784	0.000*	0.57	0.000*
Monocytes/HDL-C	0.766	0.000*	0.459	0.002*
Monocytes/LDL-C	0.606	0.003*	-0.091	0.554
Monocytes/Total cholesterol	0.246	0.270	0.247	0.102
Neutrophil/HDL-C	0.753	0.000*	0.532	0.000*
Neutrophil/LDL-C	0.578	0.005*	0.077	0.616
Neutrophil/Total cholesterol	-0.184	0.413	-0.121	0.428
Platelets/HDL-C	0.766	0.000*	0.594	0.000*
Platelets/LDL-C	0.655	0.001*	0.342	0.021*
Platelets/Total cholesterol	-0.335	0.128	0.157	0.302

HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol. *p<0.05 was considered significant.

to become surrogate marker of systemic inflammation in dialysis patients.(16) Other study suggested that NLR could be used to provide information related to inflammatory condition in both HD and non-HD CKD patients.(17) Platelet/lymphocyte ratio (PLR) was suggested by other study to become a superior surrogate marker of inflammation in stage 5 CKD compare to NLR.(18) Instead of looking for new inexpensive biomarkers, these studies suggested the potential reutilizing of established routine clinical laboratory tests such as CBC to become surrogate markers for inflammation in CKD. Therefore, in this study, we investigated the potential of CBC parameters and cholesterol profile parameters to become surrogate markers for inflammation and oxidative stress in CKD patients, both in HD and non-HD.

Regarding to the cholesterol profiles, instead of using fasting cholesterol profiles, we measured non-fasting cholesterol profiles. Although fasting cholesterol profiles is measurement that used conventionally, a recent consensus from European Federation of Clinical Chemistry and Laboratory Medicine, the European Atherosclerosis Society, the British National Clinical guideline and the new Canadian guideline recommends that fasting is not routinely required for cholesterol profile measurement.(19-21) The non-fasting measurement of cholesterol profiles has some benefits such as providing easier and simpler procedure for patients since patients are able to eat normally. Since this test could be performed any time regardless the time, it may prevent long waiting times for patients. This test condition also allows health providers to determine the cholesterol profiles at random moment. Large scale studies showed that cholesterol profile is only minimally affected after habitual food intake.(19,22,23)

Since inflammation and oxidative stress appears to increase along with the advancement of CKD (24), in this cross-sectional study, participants were classified into two groups based on their hemodialysis status. This previous result was concordance with result of our study. In our study, HD group showed higher inflammation and oxidative stress compare to non-HD group as shown by higher level of hs-CRP and MDA.

This study showed that HD patients exhibited higher hs-CRP and MDA level. This confirmed the finding of numerous study demonstrating the additional inflammation and oxidative stress burden in HD compared to non-HD patients. The mechanism of inflammatory states in CKD patients is suggested to be multifactorial related to immune system activation. Increased cytokine release, platelet activation, and activated pro-oxidation cascade are thought to be some of the determiner of both inflammation and oxidative stress in CKD.

To partially examine some the contribution of the immune system activation and pro-oxidative states, we measured CBC parameters and non-fasting cholesterol profiles which related to the aforementioned mechanism and performed correlation tests with CRP, as marker of inflammation and MDA, as marker of oxidative stress. Our results showed that in the HD group, total cholesterol/HDL-C ratio was strongly associated with CRP and MDA. Combination between monocyte or neutrophil or platelet and HDL-C (monocyte/HDL-C ratio), neutrophil/HDL-C ratio, and platelet/HDL-C ratio) were also strongly associated with hs-CRP and MDA. These results showed the potential of combination of CBC parameters and non-fasting cholesterol profile to describe inflammation and oxidative stress in CKD patients receiving routine hemodialysis therapy. However, in the non-HD group, combination of these parameters only showed weak or moderate association with hs-CRP and MDA.

The association of platelet/HDL-C ratio with inflammation and oxidative stress might stem from the platelet activation which is common in CKD. The platelet activation is one among the key factors in atherosclerotic formation. In the initial stage of atherosclerotic formation, activated platelet aggregate in the vascular endothelia and attract HDL-deficient monocytes (25). The accumulated monocytes and phospholipids in the vascular wall then transform into plaques that ignite further inflammatory response.(25)

The association of monocyte/ or neutrophil/HDL-C ratio with inflammation and oxidative stress marker might be explained by the fact that both monocyte and neutrophil are highly involved in the initiation of immune response. The differentiated monocytes are carried Toll-like receptors (TLRs) and scavenger receptors which recognize pathogen-associated molecular patterns (PAMPs) to remove microorganisms, lipids, and dying cells via phagocytosis. Subsequently, these cells produce cytokines as well as superoxide that attract more immunocompetent cells such as neutrophils to the sites of inflammation.(26) Together, the monocytes and neutrophils produce more cytokines including hs-CRP, interleukin (IL)-6, and interferon (IFN)-γ that reinforce the inflammation in CKD patients (26).

On the other hand, dysregulation of HDL synthesis and degradation is prevalent in CKD patients. Normal HDL carries anti-oxidant and anti-inflammatory properties

which mediated by paraoxane and glutathione peroxidase. In CKD where the pro-oxidative factors are dominant, oxidative modification of phospholipid are occurrent.(27) The phospholipid medification may inhibit the anti-oxidant and anti-inflammatory properties of HDL.(27) Therefore, in this study, HDL was inversely associated with hs-CRP and MDA as represented in monocyte/, neutrophil/, and platelet/ HDL-C ratio.

The findings of this study should be viewed with some limitations. The small sample size of this study might not reflect accurately the capacity of CBC parameters and cholesterol profile to become surrogate marker for hs-CRP and MDA for evaluating inflammation and oxidative stress in CKD patients.

Another limitation of this study is its applicability. The relatively weak association between CBC parameters and cholesterol profile with CRP and MDA in non-HD limited its use in the daily practice. However, this study is able to confirm the previous finding that oxidative stress markers is increased particularly in HD patients. (28) The association between CBC parameters and cholesterol profile with hs-CRP and MDA indicates that some routinely examined parameters may represent or predict the inflammation and oxidative stress in CKD, which was demonstrated previously. (29)

Conclusion

Some CBC parameters and non-fasting cholesterol profile such as cholesterol/HDL-C, monocyte/HDL-C, neutrophil/ HDL-C and platelet/HDL-C ratio were strongly associated with the level of hs-CRP and MDA. Further study with higher number of subjects is needed to assess whether this parameter represent prognostic value among CKD patients.

Acknowledgement

This research is funded by RISET MANDAT grant by Universitas Airlangga. We also thank Prodia Clinical Laboratory and Mr. Faris Triyanto for the technical support.

References

1. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco M V, *et al.* Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000; 58: 353-62.
2. Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007; 116: 85-97.
3. Stenvinkel P, Gillespie IA, Tunks J, Addison J, Kronenberg F, Drueke TB, *et al.* Inflammation modifies the paradoxical association between body mass index and mortality in hemodialysis patients. J Am Soc Nephrol. 2016; 27: 1479-86.
4. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, *et al.* Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107: 499-511.
5. Atamer A, Kocyigit Y, Ecder SA, Selek S, Ilhan N, Ecder T, *et al.* Effect of oxidative stress on antioxidant enzyme activities, homocysteine and lipoproteins in chronic kidney disease. J Nephrol. 2008; 21: 924–30.
6. Stanifer JW, Muiru A, Jafar TH, Patel UD. Chronic kidney disease in low-and middle-income countries. Nephrol Dial Transplant. 2016; 31: 868-74.
7. Guthrie GJK, Charles KA, Roxburgh CSD, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil–lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013; 88: 218-30.
8. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med. 2012; 5: 2. doi: 10.1186/1755-7682-5-2.
9. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research. Philadelphia: Lippincott Williams & Wilkins; 2011.
10. Yilmaz G, Sevinc C, Ustundag S, Yavuz YC, Hacıbekiroglu T, Hatipoglu E, *et al.* The relationship between mean platelet volume and neutrophil/lymphocyte ratio with inflammation and proteinuria in chronic kidney disease. Saudi J Kidney Dis Transplant. 2017; 28: 90-4.
11. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, *et al.* KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014; 63: 713-35.
12. Keddis MT, Amer H, Voskoboev N, Kremers WK, Rule AD, Lieske JC. Creatinine-based and cystatin C-based GFR estimating equations and their non-GFR determinants in kidney transplant recipients. Clin J Am Soc Nephrol. 2016; 11: 1640-9.
13. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. J Clin Invest. 2006; 116: 288-96.
14. Xu G, Luo K, Liu H, Huang T, Fang X, Tu W. The progress of inflammation and oxidative stress in patients with chronic kidney disease. Ren Fail. 2015; 37: 45-9.
15. Welsh P, Preiss D, Tsiropoulou S, Rios FJ, Harvey A, Dulak-Lis MG, *et al.* Biomarkers of vascular inflammation and cardiovascular disease. In: Berbari A, Mancia G, editors. Arterial Disorders. Berlin: Springer; 2015. p. 115-36.
16. Malhotra R, Marcelli D, von Gersdorff G, Grassmann A, Schaller M, Bayh I, *et al.* Relationship of neutrophil-to-lymphocyte ratio and serum albumin levels with C-reactive protein in hemodialysis patients: results from 2 international cohort studies. Nephron. 2015; 130: 263–70.
17. Okyay GU, İnal S, Öneç K, Er RE, Paşaoğlu Ö, Paşaoğlu H, *et al.* Neutrophil to lymphocyte ratio in evaluation of inflammation in patients with chronic kidney disease. Ren Fail. 2013; 35: 29-36.

18. Turkmen K. Platelet-to-lymphocyte ratio: one of the novel and valuable platelet indices in hemodialysis patients. Hemodial Int. 2013; 17: 670. doi: 10.1111/hdi.12095.
19. Nordestgaard BG, Langsted A, Mora S, Kolovou G, Baum H, Bruckert E, *et al.* Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J. 2016; 37: 1944-58.
20. Schnabel E, Anderson JM, Farquhar MG. The tight junction protein ZO-1 is concentrated along slit diaphragms of the glomerular epithelium. J Cell Biol. 1990;111: 1255-63.
21. Waters DD, Boekholdt SM. An evidence-based guide to cholesterol-lowering guidelines. Can J Cardiol. 2017; 33: 343-9.
22. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation. 2008; 118: 2047-56.
23. Langsted A, Nordestgaard BG. Nonfasting lipids, lipoproteins, and apolipoproteins in individuals with and without diabetes: 58 434 individuals from the Copenhagen General Population Study. Clin Chem. 2011; 57: 482-9.
24. Dounousi E, Papavasiliou E, Makedou A, Ioannou K, Katopodis KP, Tselepis A, *et al.* Oxidative stress is progressively enhanced with advancing stages of CKD. Am J Kidney Dis. 2006; 48: 752-60.
25. Landray MJ, Wheeler DC, Lip GYH, Newman DJ, Blann AD, McGlynn FJ, *et al.* Inflammation, endothelial dysfunction, and platelet activation in patients with chronic kidney disease: the chronic renal impairment in Birmingham (CRIB) study. Am J kidney Dis. 2004; 43: 244-53.
26. Yang J, Zhang L, Yu C, Yang X-F, Wang H. Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases. Biomark Res. 2014; 2: 1. doi: 10.1186/2050-7771-2-1.
27. Vaziri ND, Navab M, Fogelman AM. HDL metabolism and activity in chronic kidney disease. Nat Rev Nephrol. 2010; 6: 287-96.
28. Thaha M, Yusuf M, Empitu MA, Bakarman A, Tomino Y. Distribution of dimethylarginine-dimethylaminohydrolase-II (DDAH2) gene polymorphism in hemodialysis patients. Acta Med Indones. 2013; 45: 83-8.
29. Thaha M, Empitu MA, Kadariswantiningsih IN, Nugroho CW, Hasanatuludhhiyah N, Rasyid H, El Hakim Z, Suryansyah MM, Alda RR, Alsagaff MY, Amin M. Anthropometry-based Body Fat Percentage Predicts High hs-CRP in Chronic Kidney Disease Patients. Indones Biomed J. 2018; 10: 184-91.