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Evaluating Cardiovascular Risk in Chronic Kidney Disease Patients: A Biomarker Approach

(Menilai Risiko Kardiovaskular pada Pesakit Buah Pinggang Kronik: Pendekatan Penanda Biologi)

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ABSTRACT

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in chronic kidney disease (CKD) patients. This study aimed to determine the roles of CVD biomarkers in CKD patients. This was a case-control study which recruited consecutive patients with stage 2-4 CKD patients with and without CVD. Serum levels of highly-sensitive C reactive protein (hs-CRP), cystatin C (CysC), asymmetrical dimetylarginine (ADMA) and symmetrical dimethylarginine (SDMA) were measured. Sixty two stage 2-4 CKD patients with a mean age of 60.3 ± 10.4 years were recruited. Twenty three (37.1%) of them had CVD. Those CKD patients with CVD were older (64.1±8.0 vs 58.1± 1.1, $p<0.05$*) and had significantly higher systolic blood pressure (139.4 ± 16.2 vs 129.4 ± 14.8 mmHg,* $p<0.05$*). Diabetic patients had 8 times (95% CI 1.25-51.77,* $p< 0.05$*) higher risk to develop CVD. CKD patients with CVD had a higher serum creatinine (185.0 ± 54.1 vs 154.1 ± 54.4 µmol/L,* $p<0.05$*), a lower estimated glomerular filtration rate (33.7 ± 12.2 vs 42.2 ± 14.5 mL/min/1.73m²* $p<0.05$*) and a lower triglyceride levels (1.3 (1.1-1.7) vs 1.8 (1.4-2.3) mmol/L,* $p<0.05$*), compared to those without CVD. Fasting blood sugar was 7.1 ± 2.7 mmol/L in CVD group and 6.3 ± 1.6 mmol/L in non CVD group (*$p>0.05$*). There were no differences in their mean serum levels of hs-CRP, CysC, ADMA and SDMA. Risk factors including age, diabetes mellitus, hypertension and renal functions were still the most important CVD risk factors in CKD patients.*

Keywords: Asymmetrical dimetylarginine; biomarker; cardiovascular disease; chronic kidney disease; cystatin C

ABSTRAK

Penyakit kardiovaskular (CVD) adalah punca utama morbiditi dan kematian kepada pesakit buah pinggang kronik (CKD). Kajian ini bertujuan untuk menentukan peranan penanda biologi kardiovaskular dalam kalangan pesakit CKD. Ini adalah satu kajian kes-kawalan yang melibatkan pesakit CKD peringkat 2-4 dengan dan tanpa CVD. Tahap serum protein reaktif C sensitif berdaya tinggi (hs-CRP), sistatin C (CysC), asimetri dimetilarginin (ADMA) dan simetri dimetilarginin (SDMA) diukur. Enam puluh dua pesakit CKD peringkat 2-4 dengan purata umur 60.3 ± 10.4 tahun telah diambil. Dua puluh tiga (37.1%) daripada mereka mempunyai CVD. Pesakit CKD dengan CVD yang lebih tua (64.1 ± 8.0 berbanding 58.1 ± 1.1, $p<0.05$*) dan mempunyai tekanan darah sistolik yang lebih tinggi (139.4 ± 16.2 berbanding 129.4 ± 14.8 mmHg,* $p<0.05$*). Seperti yang dijangka pesakit kencing manis mempunyai 8 kali (95% CI 1.25-51.77,* $p<0.05$*) risiko yang lebih tinggi untuk mendapat CVD. Pesakit CKD dengan CVD mempunyai nilai serum kreatinin yang lebih tinggi (185.0 ± 54.1 berbanding 154.1 ± 54.4 µmol/L,* $p<0.05$ *lebih rendah anggaran kadar penapisan glomerul (33.7 ± 12.2 berbanding 42.2 ± 14.5 mL/min/1.73 m2,* $p<0.05$ *dan tahap trigliserida yang lebih rendah (1.3 (1.1-1.7) berbanding 1.8 (1.4-2.3) mmol/L,* $p<0.05$*) berbanding dengan mereka yang tidak mempunyai CVD. Paras gula berpuasa adalah 6.8 ± 2.5 mmol/L di dalam kumpulan CVD dan 7.0 ± 2.9 mmol/L dalam kumpulan bukan CVD (*$p>0.05$*). Tidak ada perbezaan dalam tahap serum hs-CRP, CycC, ADMA dan SDMA mereka. Kesimpulan daripada kajian ini adalah faktor risiko CVD tradisi seperti umur, penyakit kencing manis, darah tinggi dan fungsi buah pinggang masih adalah faktor risiko CVD yang paling penting dalam pesakit CKD.*

Kata kunci: Asimetri dimetilarginin; sistatin C; penanda biologi; penyakit buah pinggang kronik; penyakit kardiovaskular

INTRODUCTION

Cardiovascular disease (CVD) is one of the most important causes of worldwide preventable morbidity and mortality (Hennekens 1998). CVD has become the major cause of mortality in Malaysia and mortality rates due to CVD continue to rise (Khor 2001; WHO 2014). Epidemiological studies have identified many major clinical risk factors for CVD which include diabetes mellitus, hypertension, dyslipidaemia and smoking. Despite measures to control these risk factors and advances in therapeutic measures, CVD mortality continues its relentless rise. Hence CVD and its treatment as well as the treatment/prevention of its risk factors pose a huge economic burden to our country. Patients with chronic kidney disease (CKD) have an unacceptably high prevalence and incidence of CVD. CKD patients, regardless of age, race, or gender, suffer from

a 10- to 100-fold greater incidence of death from CVD compared to their normal counterparts in the general population. Moreover, 39% of CKD patients have had a previous history of CVD (Sarnak et al. 2003). Many authors believe that CKD itself is a cardiovascular disease equivalent (Tonelli et al. 2001). Risk factors that are uniquely associated with CKD include anaemia, left ventricular hypertrophy, hypoalbuminaemia and deranged calcium-phosphate metabolism. Additionally, there is now much evidence to indicate that CKD itself is a chronic low-grade proinflammatory state that promotes atherosclerosis and CVD. Inflammatory biomarkers such as highly-sensitive C reactive protein (hs-CRP), cystatin C (CysC) and more recently, asymmetrical dimetylarginine (ADMA) and symmetrical dimethylarginine (SDMA) were being investigated as CVD marker in CKD patients (Abraham et al. 2009; Carmen et al. 2011; Schwedhelm et al. 2011; Zoccali et al. 2001).

CRP is a protein well established to decrease endothelial nitric oxide synthase expression and contributes to the development of atherosclerosis. CKD patients demonstrate signs of inflammation even before the initiation of dialysis. There are a strong relationships between renal function and various inflammatory biomarkers, such as CRP, IL-6 and TNF-a, suggesting that the kidney plays a role in the clearance of pro-inflammatory cytokines (Descamps-Latscha & Witko-Sarsat 2001; Pecoits-Filho et al. 2002). CysC is a 122-amino acid that belongs to a family of potent, noncovalent, competitive inhibitors of mammalian lysosomal cysteine proteinases. Unlike serum creatinine, CysC has a constant rate of production independent of age, sex or muscle mass and may be a better marker for renal function (Coll et al. 2000; Marwyne et al. 2011; Moran et al. 2008). Several recent publications have also demonstrated that CysC was superior to serum creatinine for prediction of all-cause mortality, cardiovascular events and incident congestive heart failure in elderly community-based cohorts (Joachim et al. 2007).

ADMA is a natural endogenous inhibitor for nitric oxide production which is a vasculo-protective substance. By inhibiting nitric oxide formation, ADMA causes endothelial dysfunction, vasoconstriction, hypertension and worsening of atherosclerosis. Levels of ADMA and its isomer SDMA, which does not inhibit nitric oxide synthesis, are both elevated in patients with kidney disease. Data from prospective clinical trials in patients with CKD suggest that ADMA is an independent marker of progression of renal dysfunction, vascular complications, cardiovascular disease and death (Schwedhelm et al. 2011; Zoccali et al. 2001).

Unfortunately, as CKD is a heterogenous disease with many comorbidities, there was no single biomarker had been used as a surrogate marker for CVD in CKD patients in clinical setting. Usually the detection for CVD in CKD patients will only be done when the patients are symptomatic and too late. Hence, it is important to find a suitable CVD biomarker in CKD patients so prevention and treatment can be institute early. The objectives of this study were to determine serum levels of hs-CRP, CysC, ADMA and SDMA in patients with CKD with and without CVD. We also wanted to determine the association between these biomarkers with different stages of CKD.

Patients and Methods

This was a case-control study between CKD patients with and without CVD. The patients were matched based on their stages of CKD and comorbidities i.e. diabetes mellitus, hypertension, dyslipidaemia and history of smoking. Both control and the case patients were recruited consecutively from the nephrology clinic at Universiti Kebangsaan Malaysia Medical Centre. All consented adult patients with stage 2 to 4 CKD were eligible for this study. Pregnant patients and patients with a life expectancy less than 2 years and psychiatric disorder that might interfere with patient compliance to clinic visits were excluded from the study.

Baseline demographic data and routine blood and non-invasive cardiovascular investigations were performed as per standard care. The study proposal was reviewed, approved and granted by the Ethics and Research Committee of the Universiti Kebangsaan Malaysia Medical Centre (Study code: UKM-DLP-2011-030). Informed consents were taken from all the study patients.

Cardiovascular disease was defined when one or more of the following conditions occur: Acute coronary syndrome, ischaemic heart disease, congestive cardiac failure, transient ischaemic attack, stroke, peripheral vascular disease and abdominal angina (Shanti et al. 2011).

MEASUREMENTS METHODS

Biomarkers were measures after consents were taken from the patients. Five mL of plasma non-fasting blood samples for biomarkers levels were kept in EDTA-plasma tubes at -20^{o}C. ADMA and SDMA were measured using ELISA essay kits (Eagle Bioscience Inc, Nashua NH). Hs-CRP was measured using latex enhanced immunoturbidimetric (Roche Diagnostic Corp) using Cobra Intergral Instruments. CysC was measured using particle enhanced immunonephelometry technique on the Behring nephelometer systems

SAMPLE SIZE CALCULATION

Prior data indicated that the probability of exposure among controls was 0.2 (Schwedhelm et al. 2011). Using the formula by Kelsey, we needed a total sample size of 60 patients to be able to reject the null hypothesis that this odds ratio equals 5 with a probability power of study of 0.8.

STATISTICAL ANALYSIS

All numerical data was subjected to normality testing using Kolmogorov Smirnov. Normally distributed data was expressed as mean ± standard deviation whereas non-normally distributed data was expressed as median (interquartile range). For normally distributed data, parametric test with Students' T test was used. For non-

normally distributed data, the mean of the two groups were compared using non-parametric tests - Mann-Whitney U, Chi-Square test and Fisher's Exact test for qualitative data and data for each group was compared using analysis of variance (ANOVA). For any skewed distribution, multiple linear regressions were used. The statistical package IBM SPSS version 19.0 (IBM Corp, New York, USA) was used for the above analysis. Statistical significance was taken as $p<0.05$.

RESULTS

Sixty two CKD patients with a mean age of 60.3 ± 10.4 years were recruited, 47 patients were men and 15 patients were women. Nine had stage 2 CKD, 33 had stage 3 and 20 patients with stage 4. Of these, 23 (37.1%) had CVD, 23 (37.1%) had diabetes mellitus and 58 (93.5%) had dyslipidaemia.

Table 1 shows their baseline demographic parameters in patients with and without CVD. Patients with CVD were significantly older and had higher systolic blood pressure than patients without CVD. Other parameters were not significant between the both groups. Using multivariate logistic regression, only DM were found to be predictor of CVD (Adjusted OR: 8.04, 95% CI 1.25-51.77, $p<0.05$) (Table 2).

Table 3 shows investigations results between the 2 groups. In diabetic patients, there was no significant

TABLE 1. Demographic parameters in between CVD and non CVD groups

Parameters	CVD (n=23)	No CVD (n=39)	*p* value
Age (years)	64.1 ± 8.0	58.1 ± 11.1	0.027*
Gender (%)			
Male	19 (83)	28(72)	0.378
Female	4 (17)	11(28)	
Race (%)			
Malay	8 (35)	22(57)	0.094
Chinese	15 (65)	15(38)	
Indian	0 (0)	2(5)	
Diabetes mellitus (%)			
Yes	12(52)	11(28)	0.059
No	11(48)	28(72)	
Hypertension (%)			
Yes	21(91)	37(95)	0.581
No	2(9)	2(5)	
Dyslipidaemia (%)			
Yes	21(91)	37(95)	0.581
No	2(9)	2(5)	
Smoking status (%)			
Yes	1(4)	1(3)	0.456
No	18(78)	35(90)	
Ex-smoker	4(18)	3(7)	
RAAS blocker (%)			
Yes	13(57)	23(59)	0.850
No	10(43)	16(41)	
Statin (%)			
Yes	18(78)	28(72)	0.574
No	5(22)	11(28)	
Fibrate (%)			
Yes	5(22)	4(10)	0.215
No	18(78)	35(90)	
Systolic BP (mmHg)	139.4 ± 16.2	129.4 ± 14.8	0.018*
Diastolic BP (mmHg)	85.4 ± 13.4	80.1 ± 10.8	0.098
MAP (mmHg)	102.9 ± 14.1	96.1 ± 11.9	0.054
BMI (kg/m^2)	25.6 ± 3.7	26.8 ± 4.2	0.363

* statistically significant
RAAS: Renin-angiotensin-aldosterone system
BP: Blood pressure
MAP: Mean arterial Pressure
BMI : Body mass index

TABLE 2. Multivariate analysis of demographic parameters

Parameter	Adjusted Odd Ratio	95% CI	*p* value
Age	1.08	0.97-1.20	0.132
Gender	9.04	0.59-139.82	0.115
Diabetes mellitus	8.04	1.25-51.77	0.028*
Hypertension	0.31	0.01-12.83	0.313
Dyslipidaemia	0.64	0.00-450.10	0.893
Body mass index	0.85	0.66-1.08	0.184

* statistically significant

TABLE 3. Investigation results in between CVD and non CVD groups

Parameters	CVD (n=23)	No CVD(n=39)	*p* value
Hb (g/dL)	12.1 ± 3.2	13.2 ± 1.6	0.090
Cholesterol (mmol/L)	4.9 ± 0.7	5.4 ± 1.3	0.077
Tg (mmol/L)	1.3(1.1-1.7)	1.8(1.4-2.3)	0.020*
LDL (mmol/L)	2.8 ± 0.6	3.2 ± 1.1	0.161
HDL (mmol/L)	1.3 ± 0.4	1.3 ± 0.3	0.589
Uric acid (μmol/L)	480.9 ± 134.8	456.1± 102.7	0.438
Fasting blood sugar (mmol/L)	7.1 ± 2.7	6.3± 1.6	0.340
Creatinine (μmol/L)	185.0±54.1	154.1±54.4	0.035*
eGFR	33.7 ± 12.2	42.2 ± 14.5	0.023*
Cystatin C (mg/L)	1.8 ± 0.5	1.7 ± 0.8	0.777
hsCRP (mg/L)	3.7(0.8-7.7)	1.5(0.5-3.5)	0.246
ADMA (μmol/L)	0.86(0.77-0.92)	0.85(0.77-0.94)	0.987
SDMA (μmol/L)	1.9±0.3	1.7±0.5	0.059
Urine PCI	0.04(0.02-0.21)	0.06(0.02-0.13)	0.464

* statistically significant
Hb : Haemoglobin
Tg: Triglyceride
eGFR : estimated glomerular filtration rate in ml/min/1.73m^2
LDL : Low density lipoprotein
HDL : High density lipoprotein
Urine PCI : Urine Protein Creatinine index in g/mmol creatinine

difference between fasting blood glucose (8.2 ± 2.8 vs 7.5 ±1.8 mmol/L, *p*=0.482) and HbA1c (7.2±1.6 vs 8.1±2.0%, *p*=0.372) in between patients with CVD and non CVD, respectively. Table 4 shows the association between serum levels of hs-CRP, CysC, ADMA and SDMA with stages of CKD.

DISCUSSION

CKD is a worldwide epidemic and in Malaysia, the prevalence of all stages of CKD was about 9% and only 4% of them are aware of the diagnosis. In this study the factors associated with increase risk of CKD were age, hypertension, diabetes mellitus and dyslipidaemia (Lai et al. 2013). The prevalence of hypertension and type 2 diabetes mellitus in Malaysia for aged 30 and above was 43.5% (Clinical Practice Guidelines 2013) and 20.8% (Clinical Practice Guidelines 2015), respectively. As these rates are increasing in trend, we foresee the prevalence of CKD will increase in the future.

CVD risk is extremely high in CKD patients and CKD is regarded as CVD equivalent (Tonelli et al. 2001). In this country, main cause of mortality in dialysis patient was CVD (Wong & Ong 2013). This unique and strong relationship most probably due to a strong relationship between the two organs in cardio-renal complex and because they shared many similar risk factors like age, diabetes mellitus and hypertension.

There are few CVD risk factors that are uniquely associated with CKD include anaemia, left ventricular hypertrophy, hypoalbuminaemia and deranged calcium-phosphate metabolism. Unfortunately, diagnosing CKD patients with CVD can be very challenging. Due to a very high incidence of CVD in CKD patients, the negative predictive value of many screening diagnostic non-invasive tests were diminished. The risk of contrast induced nephropathy limited the use of CT scan angiography and coronary angiogram procedures (Herzog et al. 2011). Cardiac markers like troponin T and I in acute setting were difficult to interpret in CKD patients as these markers can be elevated in the absence of true myocardial necrosis (Herzog et al. 2011).

Does everybody with CKD need a cardiology assessment? It is very time consuming and not cost-effective. We desperately need a CVD biomarker that is specific for CKD patients. Ideally, these biomarkers should

TABLE 4. Association between the biomarkers with stages of CKD

	Stage 2	Stage 3	Stage 4	p
eGFR	63.6 ± 4.4	41.1 ±8.3	24.6 ± 3.4	<0.001
hsCRP (mg/L)	3.27± 2.87	3.21 ± 3.81	7.00 ± 11.50	0.172
CysC (mg/L)	1.05± 0.11	1.61 ± 0.65	2.21 ± 0.47	<0.001
ADMA (μmol/L)	0.76 ± 0.20	0.82 ± 0.25	0.96 ± 0.35	0.142
SDMA (μmol/L)	1.34 ± 0.38	1.81± 0.32	2.02 ± 0.43	<0.001

*statistically significant
eGFR : estimated glomerular filtration rate in mL/min/1.73 m^2

help stratify CKD patients with varying degrees of risk for CVD so that early primary preventive strategies can be more effectively implemented. In this study, we looked at few potential CVD biomarkers viz hs-CRP, ADMA, SDMA and CysC in CKD patients. We have chosen stage 2-4 CKD as we could not rule out CVD confidently in stage 5 CKD patients and we are not sure the effects of dialysis on the clearance of these new biomarkers.

In our study, age was a very important risk factor for CVD. A large cohort study of 3.6 million subjects aged more than 40 years old, age is an important independent risk factor for CVD (Savji et al. 2013). There was a clear sign that Malaysian population is moving to aging population (Wan-Ibrahim et al. 2014) and we are expecting higher prevalence of CKD and CVD in the future. Another important CVD risk factor is hypertension in particular systolic hypertension. Hypertension is well established risk factor for artherosclerotic diseases including coronary artery disease, ischaemic stroke and peripheral vascular disease. Hypertension is frequently associated with CKD and it can be the cause or the consequence of CKD (Ravera et al. 2006). Controlling blood pressure especially systolic blood pressure can be difficult in CKD patients (Coresh et al. 2001; Ravera et al. 2006; Tonelli et al. 2001). Most CKD patients are volume overload (Hung et al. 2014; Wieskotten et al. 2008) and it is a risk factor for CVD.

We did not find total cholesterol and low density lipoprotein as CVD biomarkers in our study. Instead triglyceride was found to be significant lower in CKD patients with CVD. Analyzing lipid profile can be difficult in CKD patients. Most of patients were asked to limit their protein intake and majority of them were put on statin. Only few patients were put on fibrates as fibrates may cause elevated serum creatinine. Although the importance of the elevated serum creatinine is still debatable, many nephrologists are not willing to prescribe fibrates.

We found that serum creatinine and estimated glomerular filtration rate (eGFR) were predictors of CVD. Other biomarkers were not important in predicting CVD in CKD patients. Inulin clearance has long been regarded as the gold standard for measuring GFR, but the procedure is costly, time consuming and difficult to perform (Beddhu et al. 2003). Creatinine has many advantages as a filtration marker and its measurement is cost effective (Beddhu et al. 2003). eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum ceatinine. As serum creatinine and eGFR are markers of renal function, our findings are in accordance with the evidence that CKD itself is a cardiovascular disease equivalent (Tonelli et al. 2001).

Serum CysC is a new and promising marker for kidney dysfunction (Coll et al. 2000; Marwyne et al. 2011; Moran et al. 2008). Numerous studies had found CysC to be a better marker of GFR than creatinine. We have proven that CysC is a better kidney function marker in our population especially in obese individual (Marwyne et al. 2011). There are many studies looking as CysC as a cardiac biomarker (Joachim et al. 2006; Moran et al. 2008). Unfortunately, we did not manage to prove that CysC as an important marker for CVD in CKD patients. Logically if CysC is a marker for renal function, it should be a good marker to predict CVD in CKD patients such as serum creatinine and eGFR. Our results can partly be explained as there are recent evidences showed that genetic polymorphism affect CysC plasma concentration (Akerblom et al. 2014) and CysC may not predict the development of CVD independently (Patrik et al. 2015).

We failed to show that ADMA and SDMA, the two new cardiovascular markers are important markers in our CKD population. Initial studies showed that promising findings of these endothelial marker in the pathogenesis of atherosclerotic plaque. Unfortunately, the clinical utility of these markers are still uncertain and they were not routinely measured in clinical setting. Hs-CRP plays an important role in inflammation and propagation of atherosclerotic disease. Unfortunately, we found that is not useful in predicting CVD in our CVD patients. We also found that SDMA significantly increase with worsening of renal function, nevertheless it has no effect on cardiovascular prediction. As we know renin-angiotensin-aldosterone system plays an important role in the development of vascular remodeling, atherosclerotic plaque and inflammation (Duprez 2006). Hence, the negative correlation findings in our study could be confounded by many of our patients was on renin-angiotensin-aldosterone blockers.

Surprisingly we do not see any correlation as proteinuria and CVD in our population. As we know renin-angiotensin-aldosterone blockers reduces proteinuria in CKD patients. Thus, these findings might also be because more than half the patients were on renin-angiotensin-aldosterone blockers in this study.

There were few limitations of this study. The definition of CVD in our study depended on previous history and we might miss patients with asymptomatic CVD. This study was also a small case-control study that unable to make a strong recommendation for clinical practice. Nevertheless this study was robust enough and showed that renal function measured by serum creatinine and eGFR were that most powerful predictor for CVD. Serum creatinine measurement is relatively cheap and eGFR can be calculated easily. Renal function should be the determined in all patients at risk of CVD. Patient with renal failure should be stratified to have higher risk of CVD. This finding is very important and in accordance with the recommendation that CKD is a CVD equivalent. Patient with CKD should receive initial baseline non-invasive cardiology investigation like electrocardiogram and exercise stress test.

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