S Indrayanti et al /J. Pharm. Sci. & Res. Vol. 11(7), 2019, 2549-2554

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Risk Factors for Chronic Kidney Disease: A Case-Control Study in a District Hospital in Indonesia

S Indrayanti, H Ramadaniati*, Y Anggriani, P Sarnianto, N Andayani
Faculty of Pharmacy, Pancasila University, Srengseng Sawah Jagakarsa, South Jakarta, Indonesia 12640

Abstract

Aim: This study aimed to identify the risk factors of chronic kidney disease (CKD).

Methods: A case-control study was conducted in a major district hospital in West Java, Indonesia. The control group consisted of non-CKD adult outpatients attending the clinics of the study hospital, whilst the CKD patients diagnosed less than 5 years were included in case group. The patients were interviewed using a questionnaire developed by Indonesian Research Center for Food and Medicine. Data of diagnosis and comorbidities were retrieved from medical records. Multivariate logistic regression was used to analyze the CKD risk factors.

Results: There were 75 patients included in each group. The patients ranged in age from 20 to 82 years. No considerable difference in age between the groups where overall the patients aged 53.96 ± 12.59 years. Males accounted more than half of the patients in each group. The majority of patients (≥80%) in each group were married. There was no discernible difference in level of education and type of occupation between both groups. Eleven independent variables including demographic characteristics (age, gender, marital status, education level, occupation), diagnosis and comorbidity, and lifestyle issues (behaviors associated with smoking, dietary, drug use) were used as the potential risk factors. Multivariate analysis revealed five significant risk factors: diabetes mellitus (odds ratio/OR =8.20), hypertension (OR=11.50), caffeinated beverages (OR=18.10), alcoholic drinks (OR=12.80) and carbonated/sweetened beverages (OR=9.50)

Conclusion: Shortly, diabetes mellitus and hypertension have been confirmed as CKD predictors. Consumption of unhealthy drinks is associated with increased risk of CKD.

Keywords: chronic kidney disease, risk factor, lifestyle, case control

INTRODUCTION

Chronic kidney disease has been recognized as one of serious public health issues worldwide. A meta-analysis of 100 published studies involving 112 populations revealed high global prevalence of CKD which was estimated around 11-13% with the majority at stage 3 [1]. The prevalence is predicted to increase considerably every year. CKD has become a leading cause of morbidity and mortality. It is identified as a major risk factor for developing cardiovascular diseases and premature death [2,3]. The death rate of CKD patients, in particular those with stage 3 and higher, was 13 times higher than those without CKD [4]. According to World Health Organization in its Global Burden of Diseases 2013 Report uncovered the fact that CKD was a high burden disease globally leading to approximately 800,000 death cases annually (1.5% of total death rate) [5]. In addition, each stage of CKD may result in decreased patients' health related quality of life [6]. In the context of Indonesia, data from Indonesian Basic Health Survey (*Riset Kesehatan Dasar*, Riskesdas) showed that the prevalence of CKD in 2018 was 3.8 cases per 1000 populations increasing nearly two times compared to that of 2013 [7]. It is intriguing to note that around 59% of CKD patients were in the productive age. CKD constituted top ten diseases leading to hospitalization and death among inpatients in major hospitals in Indonesia [8].

In addition to morbidity and mortality implications, CKD accounted for a major cost burden to healthcare system in many countries. In the United States of America, CKD imposed a huge financial burden with the average annual treatment cost was nearly USD 4.8 billions. This number could be higher if indirect costs (e.g. loss of productivity) were included in the calculation [2]. Similar situation was seen in other developed countries where the expenses related to CKD treatment especially for end-stage renal disease contributed to 2-3% of the total healthcare budget despite the proportion of CKD patients was less than 1% of populations [9]. Financial impact of CKD was not unique to developed countries as developing countries including Indonesia also strived to cope with the high cost of CKD. Indonesian National Healthcare and Social Security Agency reported that CKD ranked as the third high cost diseases with average annual cost of IDR 1.7 trillion (approximately USD 121 million) in 2018 [10].

It is stated previously that CKD is associated with deteriorating clinical outcomes and high financial burden. Therefore, early intervention through preventive actions is urgently required to reduce the burden. One way to prevent the incidence of CKD and retard the progression of CKD to end-stage renal disease is through identifying the factors associated with increased risk of CKD. A range of studies have reported a range of risk factors, namely susceptibility factors (e.g. ageing, family history of CKD) and initiation factors (e.g. hypertension, diabetes mellitus, autoimmune disease, urolithiasis, urinary tract infection, drug toxicity) [11-14]. The consumption of energy drinks, drug misuse and adulteration of chemical substances into herbal medicines has been reported as the CKD risk factors [11,15,16]. It has been evident that herbal medicines have been used for long time before modern medicine and their use have shown an increased trend in Indonesia [17]. Nonetheless, limited published studies of CKD risk factors were conducted in developing countries like Indonesia. Thus, this study aimed to identify the risk factors of CKD including the drug use practice predisposing individuals to CKD.

METHODS

Study design and sample

A case control study was conducted in a major teaching hospital in one of districts in West Java, Indonesia. This study was part of a multicenter study involving 10 hospitals in Indonesia in 2018. Prior to data collection, appropriate sample size estimation was calculated using hypothesis testing of the odds ratio assumption. After determining the confidence value 95% (α=5%), power 80% (β=20%), the ratio of control to case 1, the proportion of risk factor in control group/P2 5% (referring to the lowest prevalence of risk factors from Riskesdas 2013) and the lowest estimated odds ratio (OR) 2.0, the minimal sample size for each group across the multicenter study was 407 [18,19]. In order to increase the power of the multicenter study, it was determined to collect the total CKD patients meeting the inclusion criteria in each study hospital. The inclusion criteria for case group included aged >18 years and diagnosed CKD ≤ 5 years. Meanwhile, the control group was recruited from outpatients attending the clinics of the study hospital during the study period. The inclusion criteria of the control group were as follows: aged > 18 years, not diagnosed with CKD or the glomerular filtration rate value ≥ 60 ml/minutes during the study period

Data collection tool

Data were collected through interviewing the patients by using a validated questionnaire developed by Indonesian Research Center for Food and Medicine. The questionnaire was initially designed to evaluate risk factors, quality of life and socioeconomic impact of CKD in Indonesia. For purpose of the present study, the quality of life and socioeconomic impact-related questions were not included. The questions in the questionnaire were divided in three sections: demographic (age, gender, marital status, level of education, type of occupation), diagnosis and comorbidities, and lifestyle (smoking habit, source of drinking water, consumption of unhealthy food, consumption of unhealthy drinks, use of over-the-counter medicine and traditional medicine). Patients' medical records were retrieved to verify the information associated with diagnosis and comorbidities. The study was approved by the Human Ethics Committee of the study hospital. Written informed consent was obtained from the patients prior to interview.

Statistical analysis

Patient characteristics, diagnosis and lifestyle data were summarized using descriptive statistics. Bivariate and multivariate logistic regression analysis using a backward likelihood ratio method was employed to identify the risk factors of CKD. Variables with significant p-value from bivariate analysis were subsequently included in the multivariate analysis. The odds ratios (OR) and their significance levels were calculated for each included independent variable. Significant variables ($p<0.05$) in the multivariate regression analysis were considered as dominant CKD risk factors. Statistical data analysis was undertaken using Statistical Product and Service Solutions (SPSS) for Windows version 23.0.

RESULTS AND DISCUSSION

There were 75 patients observed in each group during the three-month study period. Patients' demographic characteristics are detailed in Table 1. As seen in Table 1, the patients ranged in age from early twenties to more than 80 years. No considerable difference in age between the two groups. When combining the two groups, on average the patients aged 53.96 ± 12.59 years. It appeared that ageing was associated with increased CKD prevalence. More males were documented in case group (60.0%) and control group (53.3%). The majority of patients (≥80%) in each group were married. There was no discernible difference in highest level of education and type of occupation between both groups where more than half of the patients in each group were senior high school graduates and workers with physical-based occupations e.g. factory laborers, construction workers.

Information on comorbidities and life style issues are shown in Table 2. Hypertension and diabetes mellitus accounted for the most common comorbidities in each group. Expectedly, the proportion of the two comorbidities was higher in case group than its counterpart. Further, nearly a quarter of the patients in the control group did not have any comorbidity and surprisingly around 5% of the CKD patients reported no comorbidities. With respect to lifestyle issues, more than 60% of patients in control group never smoked, whilst the proportion was much lower in the case group (44.0%). It is interesting to note that patients in both groups predominantly consumed high salt and high fat food signifiying lack of healthy lifestyle implementation. There were similar proportion of patients in each group that consumed high sugar or carbonated drinks, yet there were more caffeine drinkers were reported in case group. In addition, more than half of patients in the two groups used underground water (i.e. from wells) for their daily consumption. Regarding the behaviors related to medicine use, the use of over-the-counter non-steroid anti-inflammatory drugs/NSAIDs (e.g. paracetamol, ibuprofen) were prevalent as 40% of CKD patients and more than 50% of patients in control group took the medicines for varying reasons. Noteworthy, more than half of the CKD patients reported no consumption of any modern and traditional medicines prior to diagnosis. Nearly quarter of patients with CKD consumed suspected adulterated herbal drinks and they experienced rapid relief after consuming the herbal drinks.

There were 11 independent variables used as the potential risk factors. Bivariate logistic regression was undertaken for each independent variables (Table 3). There were four variables which met the criteria for inclusion ($p<0.25$) and were retained for multivariate logistic regression analysis as follows: comorbidities, smoking habit, consumption of unhealthy drinks and consumption of OTC medicine or herbal medicine. Of four variables, there were two variables significantly predicting the occurrence of CKD, namely comorbidities and consumption of unhealthy drinks (Table 4).

Table 1. Demographic Characteristics of Patients in Case Group and Control Group

Variables	Case Group (N=75)	Control Group (N=75)
Age in years, N (%)		
≤30	4 (5.3)	2 (2.7)
31-40	5 (6.6)	6 (8.0)
41-50	10 (13.3)	13 (17.3)
51-60	28 (37.3)	24 (32.0)
>60	28 (37.3)	30 (40.0)
Mean ± SD (Range)	51.83 ± 11.65 (23-72)	56.09 ± 13.19 (20-82)
Gender, N (%)		
Male	45 (60.0)	40 (53.3)
Female	30 (40.0)	35 (46.7)
Marital Status, N(%)		
Single	3 (4.0)	2 (2.7)
Married	6 (8.0)	13 (17.3)
Widowed	66 (88.0)	60 (80.0)
Level of Education, N (%)		
Primary	3 (4.0)	2 (2.7)
Lower secondary	16 (31.3)	21 (28.8)
Upper secondary	40 (53.3)	38 (50.7)
Academy/university	16 (21.3)	14 (18.7)
Occupation, N (%)		
Knowledge-intensive	19 (25.3)	14 (18.7)
Physical-intensive	41 (54.7)	38 (50.7)
Retired	14 (18.7)	21 (28.0)
Unemployed	1 (1.3)	2 (2.7)

SD = Standard deviation

Table 2. Information on Comorbidities and life Style Issues

Variables	Case Group (N=75)	Control Group (N=75)
Comorbidities, N (%)		
Diabetes Mellitus	22 (29.3)	19 (25.3)
Hypertension	40 (53.3)	23 (30.7)
Cardiovascular Diseases	5 (6.7)	9 (12.0)
Bone Disorders	2 (2.7)	3 (4.0)
Anemia	2 (2.7)	3 (4.0)
None	4 (5.3)	18 (24.0)
Smoking Habit, N (%)		
Current Smokers	14 (18.7)	10 (13.3)
Ex-Smokers	28 (37.3)	17 (22.7)
Never Smoked	33 (44.0)	48 (64.0)
Consumption of Unhealthy Food, N (%)		
High in Salt and Fat		
High in Fat	48 (64.0)	39 (52.0)
High in Salt	7 (9.3)	13 (17.3)
Never consumed	19 (25.3)	19 (25.3)
	1 (1.3)	4 (5.3)
Consumption of Unhealthy Drinks, N (%)		
Alcoholic Drinks		
High in Sugar/Carbonated Drinks	6 (8.0)	4 (5.3)
Caffeinated Drinks	36 (48.0)	36 (48.0)
Never Consumed	28 (37.3)	14 (18.7)
	5 (6.7)	21 (28.0)
Source of Drinking Water, N (%)		
Piped Water	3 (4.0)	9 (12.0)
Underground Water	45 (60.0)	41 (54.7)
Bottled Water	27 (36.0)	25 (33.0)
Consumption of Over-the-Counter Medicine or Herbal Medicine, N (%)		
Non-Steroid Anti-Inflammatory Drugs	30 (40.0)	40 (53.3)
Chinese Herbals	1 (1.3)	3 (4.0)
Indonesian Herbal Drinks/*Jamu*	8 (10.7)	14 (18.7)
Indonesian Herbal Drinks with Suspected Chemical Adulterants	18 (24.0)	5 (6.7)
Never Consumed	18 (58.1)	13 (41.9)

Table 3. Bivariate Logistic Regression Coefficients of Candidate Variables

Variables	P-Value	Odds Ratio (95% Confidence Interval)
Age in years		
≤30	0.539	1
31-40	0.777	0.40 (0.10-5.47)
41-50	0.466	0.60 (0.07-3.22)
51-60	0.553	1.10 (0.09-3.46)
>60	0.249	0.90 (0.59-2.08)
Gender		
Male	0.410	1.30 (0.68-2.50)
Female		1
Marital Status		
Single	0.739	1.40 (0.22-8.44)
Married	0.098	0.40 (0.15-1.17)
Widowed	0.231	1
Level of Education		
Primary	0.782	1.30 (0.33-21.9)
Lower secondary	0.412	0.70 (0.54-8.57)
Upper secondary	0.848	0.90 (0.39-2.14)
Academy/university	0.788	1
Occupation		
Knowledge-intensive	0.433	2.70 (0.22-32.90)
Physical-intensive	0.537	2.10 (0.18-24.70)
Retired	0.821	1.40 (0.11-16.10)
Unemployed	0.463	1
Comorbidities		
Diabetes Mellitus	0.009	5.20 (1.50-18.10)
Hypertension	0.001	7.80 (2.36-25.94)
Cardiovascular Diseases	0.243	2.50 (0.53-11.65)
Bone Disorders	0.303	3.00 (0.37-24.29)
Anemia	0.303	3.00 (0.37-24.29)
None	0.019	1
Smoking Habit		
Current Smokers	0.132	2.00 (0.58-3.20)
Ex-Smokers	0.022	2.40 (1.13-5.06)
Never Smoked	0.049	1
Consumption of Unhealthy Food		
High in Salt and Fat	0.162	5.00 (0.58-2.71)
High in Fat	0.527	2.20 (0.18-1.11)
High in Salt	0.234	4.00 (0.40-39.10)
Never consumed	0.241	1
Consumption of Unhealthy Drinks		
Alcoholic Drinks	0.024	6.30 (1.27-26.90)
High in Sugar/Carbonated Drinks	0.009	4.20 (1.42-12.30)
Caffeinated Drinks	0.000	8.40 (2.61-26.90)
Never Consumed	0.004	1
Source of Drinking Water		
Piped Water	0.104	0.30 (0.75-1.27)
Underground Water	0.963	1.10 (0.51-2.02)
Bottled Water	0.226	1
Consumption of Over-the-Counter Medicine or Herbal Medicine		
Non-Steroid Anti-Inflammatory Drugs	0.160	0.50 (0.23-1.27)
Chinese Herbals	0.240	0.30 (0.02-2.58)
Indonesian Herbal Drinks/*Jamu*	0.123	0.40 (0.13-1.27)
Indonesian Herbal Drinks with Suspected Chemical Adulterants	0.125	2.60 (0.76-8.81)
Never consumed	0.025	1

Table 4. Multivariate Logistic Regression with Significant Independent Variables

Variables	P-Value	Odds Ratio (95% Confidence Interval)
Comorbidities		
Diabetes Mellitus	0.007	8.20 (1.75-37.70)
Hypertension	0.001	11.50 (2.68-49.60)
Cardiovascular Diseases	0.180	3.60 (0.55-22.80)
Bone Disorders	0.358	3.50 (0.24-50.60)
Anemia	0.234	5.20 (0.34-80.60)
None	0.036	1
Consumption of Unhealthy Drinks		
Alcoholic Drinks	0.020	12.80 (1.48-110.60)
High in Sugar/Carbonated Drinks	0.001	9.50 (2.52-36.10)
Caffeinated Drinks	0.000	18.10 (4.26-77.20)
Never Consumed	0.001	1

As detailed in Table 4, two comorbidities i.e. diabetes mellitus and hypertension were dominant risk factors for CKD. When holding all other variables constant, the odds of having CKD amongst patients with diabetes mellitus was approximately 8 times higher than non-diabetic patients. Hypertensive patients were nearly twelve times more likely to experience CKD in their life. The results also uncovered that patients with history of consuming unhealthy drinks corresponded with increased risk to have CKD with OR ranging between 10-12 times.

The results of this present study were consistent with the existing literature highlighting diabetes mellitus and hypertension as dominant risk factors for CKD [20-23]. These two comorbidities are classified as initiation and progression risk factors. Poor glycemic control may result in a range of renal structure alterations initiated from thickening of glomerular basement membrane which parallels with capillary and tubular basement membrane thickening [20]. The majority of DM patients demonstrate the classic pattern of glomerular hyperfiltration which then progress to persistent albuminuria and glomerular filtration rate (GFR) decline. As GFR declines, CKD complication may develop e.g. anemia, bone disorder, electrolyte imbalance [24]. Meanwhile, hypertension and CKD have shown a cyclic relationship. It has been evident that uncontrolled blood pressure may predispose the development of CKD. High blood pressure may increase intraglomerular pressure and damage glomerular filtration resulting in microalbuminuria and even proteinuria [25]. Reciprocally, progressive renal disease may exacerbate hypertension as it can increase systemic vascular resistance and volume of fluid in systemic circulation [26]. Further, our study found no association between CKD and other well-described risk factors e.g. previous history of urinary tract infection and urolithiasis.

Whilst diabetes mellitus and hypertension are well-established as CKD risk factors, consumption of unhealthy drinks is not widely documented to be a risk factor for CKD. Our study uncovered carbonated or sugar-rich drinks, alcoholic beverages and caffeinated beverages had strong association with CKD with OR 9.50, 12.80 and 18.10, respectively. This finding was in line with other local studies conducted by Delima et al [11], and Hidayati et al [16] which signified the role of mineral drinks and carbonated drinks as the predictor of CKD. Similarly, consumption of carbonated beverages at least two glasses per day will double the risk of CKD according to an American study [27]. It has been thought that the content of phosphoric acid in carbonated/mineral drinks might lead to calcium phosphate deposits in kidney. Regarding the consumption of caffeinated beverage, its link with CKD is still inconclusive and remains controversial. Our study found that those consuming regular caffeinated drinks are likely to develop CKD 18 times higher than free-caffeinated drinkers. It has been thought that caffeine may cause sudden increase in blood pressure leading to increased risk of kidney disease. This insight, however, is in contrast with a meta-analysis involving nearly 15,000 respondents which found no association between caffeinated drinks (i.e. coffee) at least one cup/day and the occurrence of CKD [28]. Likewise, a community-based prospective cohort study in South Korea reported association between intake of coffee and decreased risk of CKD development [29]. Nonetheless, the possibility of caffeine protective effects should be confirmed further in a randomized clinical trial as the results were sourced from observational studies. In addition, drug use practices were not observed as the CKD predictors. It is still equivocal whether the behavior related to the use of traditional medicine and OTC NSAIDs as some studies reported varying resuts [11,16, 30-33].

There are several limitations to this study. Firstly, it is challenging to compare our findings with other studies despite numerous studies have been done to evaluate CKD risk factors. Thus, accurate comparison with other studies might be diminished due to variations in settings, design, duration, size, and method. Secondly, the life-style related behaviors were self-reported by the study participants. There was no validation to justify the patients' responses so they were subject to potential bias. Thus, the results might be different if the patients were followed closely over certain amount of time to provide the comprehensive picture of their lifestyle practices.

CONCLUSIONS

The current study adds to the body of knowledge by confirming the strong association between diabetes mellitus and hypertension, and CKD. Consumption of unhealthy beverages (e.g. caffeinated, carbonated, alcoholic beverages) serves as another CKD predictor. It is recommended that comprehensive preventive programs including healthy lifestyle practices should be implemented to reduce the CKD prevalence and its ramification.

Acknowledgements

The authors would like to thank the participants who agreed to participate in this study and Pancasila University which provided the financial support.

REFERENCES

1. Hill, N. R., Fatoba, S. T., Oke, J. L., Hirst, J. A., O'Callaghan, C. A., Lasserson, D. S., Hobbs, F. D., Global prevalence of chronic kidney disease - A systematic review and meta-analysis, *PLOS ONE*. 2016, *11*, e0158765.
2. Jha, V., Garcia, G., Iseki, K., Chronic kidney disease: global dimension and persepectives, *Lancet.* 2013, *382*, 260-72.
3. Stemer, G., Laml-Wallner, G., Kuegler, I., Poelzleitner, P., Messner, S., Steininger, S., Dolinar, E., Zehetmayer, S., Comprehensive evaluation of clinical pharmacists' interventions in a large Austrian tertiary care hospital, *Eur J Hosp Pharm*. 2012, *19*, 529-534.
4. Ojo, A., Addressing the global burden of chronic kidney disease through clinical and translational research, *Transac Am Clin Clim Assoc*. 2014, *125*, 229-46.
5. World Health Organization, *Global Health Estimates Summary tables: Death by Cause, Age and Sex*, Geneva 2013, Available at: https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html
6. Gansevoort, R. T., Correa-Rotter, R., Hemmelgarn, B. R., Jafar, T. H., Heerspink, H. J., Mann, J. F., Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms and prevention, *Lancet*. 2013, *382*, 339-52.
7. Badan Penelitian dan Pengembangan Kesehatan , *Riset Kesehatan Dasar 2018*, Kementerian Kesehatan Republik Indonesia, Jakarta 2018, Available at: www.depkes.go.id/resources/download/info-terkini/hasil-riskesdas-2018.pdf

Pusat Data dan Informasi. *Profil Kesehatan Indonesia Tahun 2013*, Kementerian Kesehatan Republik Indonesia, Jakarta 2013, Available at: http://www.depkes.go.id/resources/download/pusdatin/profil-kesehatan-indonesia/profil-kesehatan-indonesia-2013.pdf

8. Levey, A. S., Atkins, R., Coresh, J., Chronic kidney disease as a global public health problem: approaches and initiatives-a position statement from Kidney Disease Improving Global Outcomes, *Kidney Int*. 2007, *72*, 247-59.
9. Pusat Data dan Informasi, *Biaya Klaim BPJS*, Badan Penyelenggara Jaminan Sosial (Indonesian National healthcare and Social Security Agency), Jakarta 2019.
10. Delima, D., Tjitra, E., Tana, L., Halim, F. S., Ghani, L., Siswoyo, H., Idaiani, S., Andasari, L., Faktor risiko penyakit ginjal kronik: studi kasus kontrol di empat rumah sakit di Jakarta Tahun 2014, *Buletin Penelitian Kesehatan.* 2017, *45*, 17-26.
11. Echouffo-Tcheugul, J. B., Kengne, A. P., Risk models to predict chronic kidney disease and its progression: a systematic review, *PLOS Med*. 2012, *9*, 1-18.
12. Johnson, E. S., Smith, D. H., Thorp, M. L., Yang, X. Juhaeri, J. , Predicting the risk of end-stage renal disease in the population-based setting: a retrospective case-control study, *BMC Nephrol.* 2011, *12*, 1-8.
13. National Kidney Foundation, K/DOQI clinical practice gudelines for chronic kidney disease: evaluation, classification and stratification, *Am J Kidney Dis*. 2002, *39*, S1-S266.
14. Prodjosudjadi, W., Suwitra, K., Loekman, J. S. & Widiana, I. G. R,., Detection and prevention of chronic kidney disease in Indonesia: initial community screening, *Nephrol*. 2009, *14*, 669-674.
15. Hidayati, T., Kushadiwijaya, H., Suhardi, S., Hubungan antara hipertensi, merokok dan minuman suplemen energi dan kejadian penyakit ginjal kronik, *Berita Kedokteran Masyarakat.* 2008, *24*, 90-102.
16. Trade Research and Development Agency, *Indonesian herbal: the traditional therapy*, Ministry of Trade of the republic of Indonesia, Jakarta 2009, Available at: http://www.kemendag.go.id/files/profil/Herbal.pdf
17. Lemeshow, S., Hosmer, D.W., Klar, J., Lwanga, S.K., *Adequacy of sample size in health studies*, New York, John Wiley & Sons 1990, pp.16-19.
18 Badan Penelitian dan Pengembangan Kesehatan , *Riset Kesehatan Dasar 2013*, Kementerian Kesehatan Republik Indonesia, Jakarta 2013, Available at: www.depkes.go.id/resources/download/general/Hasil%20Riskesdas%202013.pdf
19. Alicic, R.Z., Rooney, M.T., Tuttle, K.R., Diabetic kidney disease, *Clin J Am Soc Nephrol.* 2017, *12*, 2032-2045.
20. Anand, S., Shivashankar, R., Ali, M. K., Kondal, D., Binukumar, B., Montez-Rath, M. E., Prevalence of chronic kidney disease in two major Indian cities and projections for associated cardiovascular disease, *Kidney Int.* 2015, *88*, 78-85.
21. Alam, A., Amanullah, F., Baig-Ansari, N., Lotia-Farrukh, I., Khan, F. S., Prevalence and risk factors for kidney disease in urban Karachi: baseline findings from a community cohort study, *BMC Res Notes.* 2014, *7*, 179-189.
22. Hasan, M., Sutradhar I, Gupta R D, M Sarker. Prevalence of chronic kidney disease in South Asia: a systematic review, *BMC Nephrol*. 2018, *291*, 1-12.
23. Retnakaran, R., Cull, C.A., Thorne, K.I., Adler, A.I., Holman, R.R., UKPDS Study Group: risk factors for renal dysfunction in type 2 diabetes, *Diabetes*. 2006, *55*, 1832-1839.
24. Matsushita, K., van der Velde, M., Astor, B.C., Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis, *Lancet*. 2010, *374*, 2073-2081.
25. Segura, J., Ruilope, L., Hypertension in moderate-to-severe nondiabetic CKD patients, *Adv Chronis Kidney Dis*. 2011, *18*, 23-27.
26. Saldana, T.M., Basso, O., Darden, R., Sandler, D.P., Carbonated beverages and chronic kidney disease, *Epidemiol*. 2007, *18*, 501-506.
27. Wijarnpreecha, K., Thongprayoon, C., Thamcharoen, N., Panjawatanan, P., Cheungpositporn, W., Association of coffee consumption and chronic kidney disease: a meta analysis, *Int J Clin Pract*. 2017, *71*, 1-5.
28. Jhee, J.H., Nam, K.H., An, S.Y., Cha, M., Lee, M., Park, S., et al., Effects of coffee intake on incident chronic kidney disease: a community-based prospective cohort study, *Am J Med*. 2018, *131*, 1482-1490.
29. Xu, Y., Patel, D.N., Ng, S.P., Retrospective Study of Reported Adverse Events Due to Complementary Health Products in Singapore From 2010 to 2016, *Front Med (Lausanne)*. 2018, *5*, 167.
30. Jha, V., Herbal medicines and chronic kidney disease, *Nephrol.* 2010, *15*, 10-17.
31. Pongsibidong, G.S., Risk factors hypertension, diabetes and consuming herbal emdicine of chronic kidney disease in DR. Wahidin Sudirohusodo Hospital in 2015, *Jurnal Wiyata*. 2016, *3*, 162-167.
32. Zhang, X., Donnan, P.T., Bell, S., Guthrie, B., Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis, *BMC Nephrol*. 2017, 18, 256.