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Risk Factors of Chronic Kidney Disease in Indonesian Patients with Diabetes Mellitus

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ABSTRACT
Chronic Kidney Disease (CKD) is a public health problem with increasing prevalence and incidence. About 1 in 3 adults with Diabetes Mellitus (DM) has CKD. This study aims to determine the risk factors for Chronic Kidney Disease in Diabetes Mellitus (CKD-DM) patients in Indonesia. A cross-sectional study was conducted with secondary data, Indonesia Basic Health Research 2018. Data analysis was carried out univariate, bivariate, and multivariate. Also, spatial analysis was carried out to map the prevalence of cases. Among 14.932 samples, the prevalence of CKD-DM in Indonesia was 1.8%. Multivariate analysis results found that gender (aPR=3.24; 95%CI 3.182-3.306), every day smoker (aPR: 2.47; 95%CI 2.415 – 2.535), someday smoker (aPR=1.93; 95%CI 1.875 – 1.987), hypertension (aPR=1.56; 95%CI 1.540 – 1.591), pre elderly (aPR=1.13 95%CI 1.098 – 1.158), elderly (aPR=0.81; 95%CI 0.790 – 0.834), exercise (aPR =1.07; 95%CI 1.055 – 1.090), and obesity (aPR=0.90; 95%CI 0.891 – 0.924) have a significant relationship with the incidence of CKD-DM in Indonesia. This study found that gender is the dominant variable in the incidence of CKD-DM in Indonesia. It is desired that healthcare providers and program makers should recognize gender differences in the progression of CKD and conduct screening program for risk factors of CKD-DM.

INTRODUCTION

Kidney disease is a systemic disease divided into acute kidney injury and chronic kidney disease.[1] Chronic Kidney Disease (CKD) is a health problem that exists in society with increasing prevalence and incidence. CKD is an abnormality in kidney structure or function that lasts for more than three months and has an impact on health. Most people are not aware that they are suffering from CKD until it is severe and requires hemodialysis or a kidney transplant to survive.[2] CKD mainly occurs in people with diabetes mellitus. It is known that around 1 in 3 adults with diabetes mellitus, either type 1 or 2, have CKD.[3]

CKD in patients with diabetes mellitus is caused by various factors, which can be categorized as modifiable and non-modifiable. Modifiable factors include age, gender, and the onset of diabetes mellitus. Aging is the most common risk factor, even in adults without diabetes, kidney function declines by approximately 1 mL/min per year after the age of 40.[4] Regarding gender, men are more susceptible to CKD associated with diabetes mellitus than women.[5] Sex hormones may influence the risk of chronic kidney failure in adults with diabetes mellitus. Women with Type 1 diabetes may experience decreased estradiol levels and increased testosterone levels, while men with Type 1 diabetes may have either increased or decreased free testosterone levels along with elevated estradiol levels.[4] Other potential mechanisms related to gender that contribute to chronic kidney disease include differences in renal hemodynamics, diet, kidney and glomerulus size, and sex-specific genetic polymorphisms.[5]

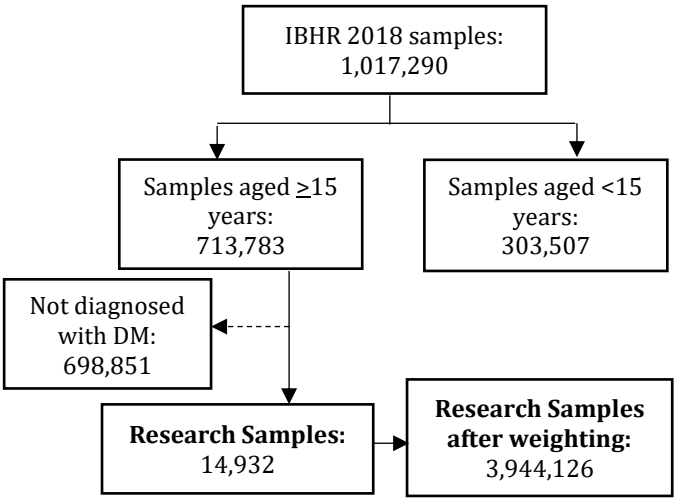
Additionally, it is known that the earliest structural changes in CKD associated with diabetes mellitus appear 1.5 to 5 years after the onset of Type 1 diabetes. Early onset of Type 2 diabetes is associated with more comorbidities and risk factors that contribute to a more rapid progression of CKD and other complications.[6] Non-modifiable risk factors for CKD include glycemic control, hypertension, lipid abnormalities, chronic inflammation, metabolic syndrome, smoking habits, physical activity/ exercise, and Advanced Glycation End-products (AGEs).[4] A study revealed that increased albuminuria is a major risk factor for developing kidney disease in individuals with diabetes mellitus. Additionally, hyperglycemia, a common condition in people with diabetes, is also a risk factor that can worsen kidney function and lead to increased AGEs.[7]

Globally, CKD in type 1 Diabetes Mellitus patients (DM patients) was responsible for 12.9 thousand incidences, 5.02 million patients, and 8.20 thousand deaths. In addition, CKD in type 2 DM patients was responsible for 2.5 million new cases, 129.56 million patients, and 405.99 thousand deaths. It is known that type 2 diabetes mellitus is the second highest cause of CKD which is associated with death. In type 2 DM patients, the prevalence of CKD varies in countries around the world, 38.8% in China, 35,52% in Ethiopia, 34.4% in India, 11.4% in Saudi Arabia, 2.2% in the United States[8], 12.8% in Vietnam, 10.0% in Thailand, 12.2% in Brunei and Malaysia, 11.1% in Cambodia, Laos, Myanmar, Philippines, and East Timor.[9] In Indonesia, the prevalence of CKD generally increased from 2.0% in 2013 to 3.8% in 2018.[10] Based on the 10th Report of The Indonesian Renal Registry in 2017, the percentage of CKD in DM patients was 21.[11]

Based on data from the Social Health Insurance Administration Body, CKD is one of the 10 catastrophic diseases with the extensive budget absorption in the National Health Insurance program.[12] Identifying high-risk groups can reduce the impact of CKD on both individuals and society.[13] One of the groups of individuals at risk of CKD is DM patients. This study aims to determine the risk factors for CKD in DM patients (Types 1 and 2) in Indonesia.

MATERIAL AND METHOD

This study used a cross-sectional study design from Indonesia Basic Health Research (IBHR) 2018, obtained from the Ministry of Health of the Republic of Indonesia. The study was conducted in October-December 2023. Respondents aged $\geq$15 years who suffered from diabetes mellitus in IBHR 2018 became the study population. The sample used for analysis was 14,932 respondents from IBHR 2018 with criteria $\geq$15 years and diagnosed with diabetes mellitus. However, weighting was carried out in data analysis to obtain a sample that was close to the population. SPSS Statistics version 25 was used for the weighting, resulting in a weighted sample of 3,944,126 (Figure 1).



Source: Indonesia Basic Health Research, 2018

Figure 1. Sampling Flow

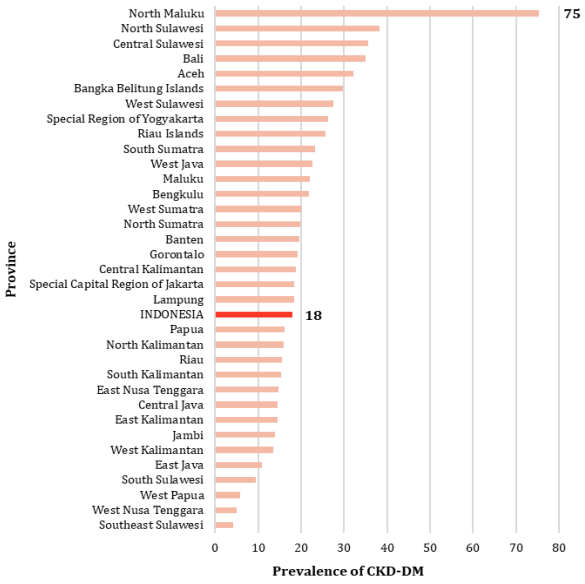
The instrument for this study is the IBHR 2018 questionnaire. The data collection process is carried out through an application and permission to use the data submitted to the Ministry of Health of the Republic of Indonesia. The status of CKD was seen from the presence of the diagnosis of CKD by a doctor. Independent variables in this study are age, gender, hypertension, smoking, exercise, and obesity. Age is categorized into teenager and adult, pre-elderly, and elderly. Smoking was categorized into the everyday smoker, someday smoker, and never smoking. Meanwhile, other variables were categorized into Yes/No.

Data analysis was carried out using the Cox regression model to determine the factors related to Chronic Kidney Disease-Diabetes Mellitus (CKD-DM) incidence. The Cox regression model was chosen to obtain a risk value. The Cox regression model needs a time variable and this study uses a cross-sectional study design, so in the multivariate analysis, a time variable is created which contains the value "1" as a null value. The first step was to carry out bivariate analysis (chi-square) to select candidate independent variables that would be included in the model. Associations between independent variables and CKD were analyzed separately. In the second step, all independent variables were entered into the model because they all had *p-value* <0.25. The adjusted prevalence ratio in the multivariate analysis was assessed at 0.05 with a 95% Confidence Interval (CI 95%). All statistical analyses used SPSS software version 25.

Spatial analysis was also carried out by mapping high-risk areas based on the prevalence ratio of CKD-DM cases in each province in Indonesia using QGIS software (ver. 3.28.4). The protocol of this study was approved by The UPN Veteran Jakarta Research Ethics Committee (419/XI/2023/KEP). All personal information was kept confidential and not reported in this paper.

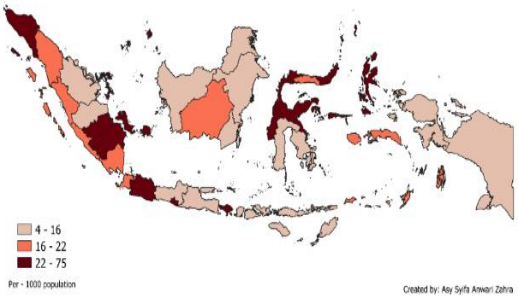
RESULTS

The prevalence of CKD-DM in Indonesia is 18 cases per 1000 population (Figure 2). Then, a distribution map of CKD-DM prevalence was created based on provinces in Indonesia. Based on the map, it was found that the lighter the map color, the lower the CKD-DM prevalence, and vice versa, the darker the map color, the higher the CKD-DM prevalence. From calculating data, it was found that the average prevalence of CKD-DM in Indonesia was 21 cases per 1000 population. The province with the lowest prevalence of CKD-DM is Southeast Sulawesi, which has 4 cases per 1000 population. Meanwhile, the province with the highest prevalence of CKD-DM is North Maluku, with 75 cases per 1000 population (Figure 3).



Source: Indonesia Basic Health Research, 2018

Figure 2. Prevalence of CKD-DM in Indonesia Based on Province



Source: Indonesia Basic Health Research, 2018

Figure 3. Distribution of CKD-DM in Indonesia by Province

Compared with the prevalence of CKD-DM in Indonesia nationwide, 14 provinces have a lower prevalence, 2 provinces have the same prevalence, and 18 provinces have a higher prevalence than the national prevalence. Provinces with prevalence higher than the national prevalence are Gorontalo, Central Kalimantan, Banten, West Sumatra, North Sumatra, Bengkulu, Maluku, West Java, South Sumatra, Special Region of Yogyakarta, Riau Islands, West Sulawesi, Bangka Belitung Islands, Aceh, Bali, Central Sulawesi, North Sulawesi, and North Maluku.

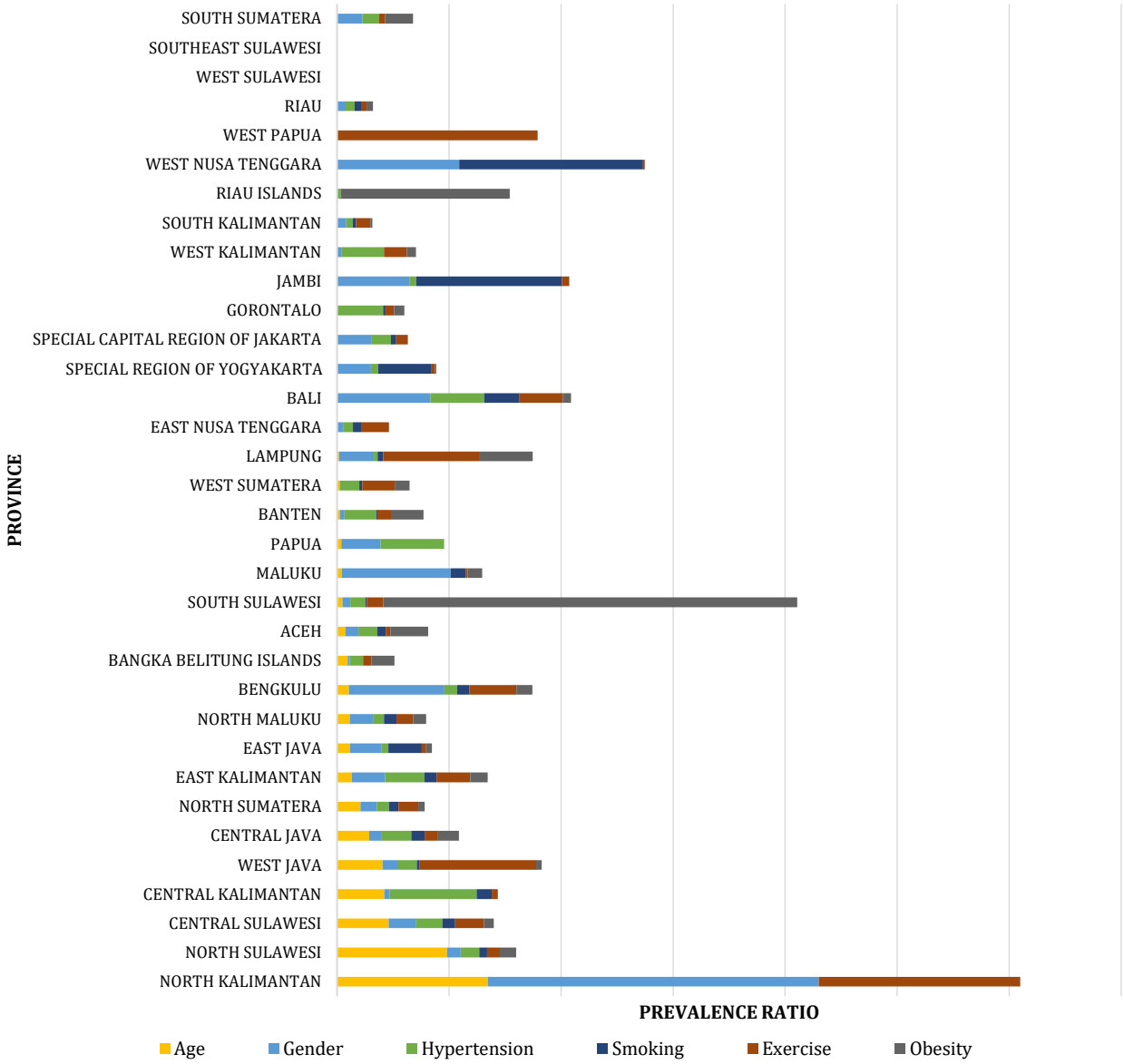
Diabetes patients who are the unit of analysis are dominated by the pre-elderly age category (50.7%). Female respondents were the most respondents with a total of 59.5%. Based on hypertension status, it was found that 54.6% of DM patients were not hypertensive. 69.7% of respondents who were DM patients never smoked, 51.9% of them did not exercise, and 66.4% of them were not obese (Table 1).

Subsequently, the Prevalence Ratio (PR) was calculated from the distribution of CKD-DM risk factors based on provinces in Indonesia to see the risk level. Based on age, gender, and exercise variables, the province with the highest risk for CKD-DM is North Kalimantan. Meanwhile, Central Kalimantan Province is at the highest risk based on the hypertension variable, West Nusa Tenggara Province is at the highest risk based on the smoking variable, and South Sulawesi Province is at the highest risk based on the obesity variable (Figure 4).

Table 1. Distribution and Frequencies of CKD-DM Risk Factors in Indonesia

Variables	n = 14,932	n (weighted) = 3,944,126	%
Age			
Elderly	5,290	1,404,660	35.6
Pre-elderly	7,632	1,999,331	50.7
Teenagers & adults	2,010	540,135	13.7
Gender			
Male	5,805	1,599,304	40.5
Female	9,127	2.344.822	59.5
Hypertension			
Yes	5,103	1,336,216	33.9
No	8,089	2,152,606	54.6
Missing system	1,740	455,304	11.5
Smoking			
Every day smoker	2,937	822,869	20.9
Someday smoker	1,280	373,965	9.5
Never smoked	10,715	2,747,292	69.7
Exercise			
No	7,870	2,046,152	51.9
Yes	7,062	1,897,974	48.1
Obesity			
Yes	4,223	1,137,010	28.8
No	10,044	2,618,789	66.4
Missing system	665	188,327	4.8

Source: Indonesia Basic Health Research, 2018



Source: Indonesia Basic Health Research, 2018

Figure 4. Risk Levels Based on Province

In the first stage (before multivariate analysis), all variables were significantly associated with CKD-DM. After multivariate analysis, the results of the study showed that gender was the variable that had the most influence on the incidence of CKD-DM, where male DM patients were 3.24 times more likely to experience CKD-DM than those of female gender. DM patients who smoke every day have a 2.47 times greater risk, and DM patients who do not smoke every day have a 1.93 times greater risk of experiencing CKD-DM than those who never smoke.

DM patients who have hypertension are 1.56 times more likely to experience CKD than those who do not have hypertension. Then, it was found that pre-elderly DM patients had a 1.13 times risk of experiencing CKD-DM compared to teenagers and adults. Meanwhile, the elderly category is a protective factor in the occurrence of CKD-DM. DM patients who do not exercise are 1.07 times more likely to experience CKD than those who exercise. The obesity variable was found to be a protective variable in the occurrence of CKD-DM with an adjusted PR of 0.90 (95% CI: 0.891 – 0.924).

Table 2. Risk Factors of CKD-DM in Indonesia

Variables	Chronic Kidney Disease				Total		*Adjusted* PR (95% CI)	*p-value*
	Yes		No					
	n	%	n	%	n	%		
Age								
Elderly	31,152	2.2	1,373,508	97.8	1,404,660	100	0.81 (0.790 – 0.834)	0.00
Pre-elderly	32,089	1.6	1,967,242	98.4	1,999,331	100	1.13 (1.098 – 1.158)	0.00
Teenagers & adults	7,407	1.4	532,728	98.6	540,135	100	Ref	
Gender								
Male	35,795	2.2	1,563,487	97.8	1,599,282	100	3.24 (3.182 – 3.306)	0.00
Female	34,851	1.5	2,309,995	98.2	2,344,846	100	Ref	
Hypertension								
Yes	32,372	2.4	1,303,865	97.6	1,336,237	100	1.56 (1.540 – 1.591)	0.00
No	33,513	1.6	2,119,097	98.4	2,152,610	100	Ref	
Smoking								
Every day smoker	11,597	1.4	811,273	98.6	822,870	100	2.47 (2.415 – 2.535)	0.00
Someday smoker	7,129	1.9	366,827	98.1	373,956	100	1.93 (1.875 – 1.987)	0.00
Never smoked	51,920	1.9	2,695,383	98.1	2,747,303	100	Ref	
Exercise								
No	37,191	1.8	2,008,990	98.2	2,046,181	100	1.07 (1.055 – 1.090)	0.00
Yes	33,454	1.8	1,864,491	98.2	1,897,945	100	Ref	
Obesity								
Yes	18,882	1.7	1,118,163	98.3	1,137,045	100	0.90 (0.891 – 0.924)	0.00
No	44,916	1.7	2,573,835	98.3	2,618,751	100	Ref	

Source: Indonesia Basic Health Research, 2018

DISCUSSION

The prevalence of CKD-DM in Indonesia is 1.8%. IBHR 2018 conducted interviews with residents aged ≥15 years regarding chronic kidney failure status. Based on the IBHR 2018 National Results Report, it was found that the prevalence of chronic kidney failure in the population aged ≥ 15 years in Indonesia based on a doctor's diagnosis was 3.8%.[10] This shows that the prevalence rate of CKD-DM is almost half the prevalence rate of chronic kidney failure in the population aged ≥ 15 years in Indonesia. This research also created a distribution map of the incidence of chronic kidney failure in Indonesia by province. Based on the mapping results, it was found that the province with the highest prevalence rate was North Maluku Province at 7.5% and the province with the lowest prevalence rate was Southeast Sulawesi Province at 0.4%. It is known that according to the IBHR 2018 results, North Maluku Province is also the province with the second highest prevalence rate of chronic kidney failure in residents aged >15 years, namely 5.6%.[10] Looking at the Provincial Report related to IBHR 2018, it was found that the prevalence of diabetes mellitus in North Maluku Province was higher, namely 1.00%,[14] when compared to the prevalence rate of diabetes mellitus in Southeast Sulawesi Province, which was 0.87%.[15] It is possible that the higher the prevalence rate of diabetes mellitus, the greater the possibility of suffering from chronic kidney failure, considering that diabetes mellitus is one of the factors associated with the incidence of chronic kidney failure.[3] From the results of the data analysis, there are 17 other provinces apart from North Maluku with CKD-DM prevalence rates above the national average or >1.8%. This should be a concern because more than half of the provinces that were currently participating in the IBHR 2018 had high prevalence rates of CKD-DM.

The final results of the multivariate analysis indicate that gender is the dominant variable in the incidence of CKD-DM in Indonesia. Oshima *et al*. (2023) also showed that men are at a 1.34 (95% CI: 1.02 – 1.075) times risk and are more likely to experience CKD-DM compared to women.[16] The difference in risk levels between men and women is likely due to the role of sex hormones. It is estimated that some of the kidney failure development in men is due to the adverse effects of testosterone, which can affect the Glomerular Filtration Rate (GFR). Conversely, previous studies have also shown

the important role of estrogen as a protective factor in women experiencing CKD-DM.[17] Therefore, the development of CKD-DM to become End-Stage Renal Disease (ESRD), a late-stage kidney disease, is faster in women. This is because women in the postmenopausal period no longer have the protection of estrogen hormones. This research shows that individuals with diabetes mellitus who smoke, whether everyday smokers or someday smokers, are at risk of experiencing chronic kidney failure. This is in line with research conducted by Nazzal, et al, (2022), where DM patients who smoke are 2.3 (95% CI: 1.3 – 4.2) times more likely to experience CKD-DM compared to non-smokers.[18] Smoking can accelerate the development of CKD-DM, especially since, according to the CDC, the percentage of smokers among DM patients was still relatively high in 2018, at 21.8%. The exact mechanism by which smoking habits mediate the development of CKD-DM is not yet clearly understood. However, it is estimated that the main triggers are sustained sympathetic activity, oxidative stress, and hyperlipidemia. These factors are closely related because diabetes mellitus is a multisystemic metabolic disease.[19]

Hypertension is also found to be a risk factor in the occurrence of CKD-DM. A case-control study conducted in Indonesia, specifically at a hospital in Surabaya by Sutadji, et al (2023), showed a similar result, where diabetic patients with hypertension are at a 3.80 times greater risk (95% CI: 1.875 – 7.706) of experiencing CKD-DM compared to those without hypertension.[20] Hypertension in CKD-DM is multifactorial, but mostly mediated by increased vasoconstriction and increased extracellular volume, which will then increase kidney performance and ultimately cause kidney damage due to overwork.[21] This study found that the pre-elderly category is more at risk of experiencing CKD-DM compared to teenagers and adults, while the elderly category becomes a protective factor. However, statistically, the Adjusted PR value generated from the study is not significant because it approaches the null value. A cohort study on the risk factors and burden of CKD-DM conducted by Xie, et.al (2023) showed a similar thing, where an increased risk of CKD-DM occurrence was found with increasing age, even after controlling for period and cohort effects. Especially in the age group of 55-59 years, diabetic patients aged 55-59 years have an 8.21 times greater risk of experiencing CKD-DM.[22] Humans are biological creatures that can experience aging, including a progressive decline in kidney function and structure. A source states that changes in kidney function during normal aging are the most dramatic changes compared to any other organ system. In addition, the mechanism behind age becoming a risk factor for CKD-DM may also be due to hormonal changes associated with aging. Such as estrogen hormone in women which functions as a protective factor decreases as women age because they begin to experience menopause.[23] Therefore, the implementation of CKD-DM screening and intervention measures according to its risk factors, namely in the elderly population (pre-elderly and elderly), needs to be done.

Not exercising also poses a greater risk of experiencing CKD than those who exercise. However, statistically, the Adjusted PR value generated from this study is not significant because it approaches the null value. Wang *et al*. (2023) showed that those who did not engage in physical activity are at a 1.78 (95% CI: 0.42 – 3.14) times risk more likely to experience CKD-DM compared to those who engaged in physical activity. The potential mechanism that may occur is that exercise or physical activity increases mitochondrial β-oxidation, thereby slowing the progression of kidney disease.[24]

Individuals with diabetes mellitus often experience progressive kidney failure. Therefore, the beneficial effects of physical activity on the prevention and early detection of kidney disease in this population may have a large clinical importance. This study found that obesity is a protective factor for CKD-DM with an Adjusted PR value of 0.90. However, the Adjusted PR is not statistically significant because it approaches the null value. Another study conducted by Xia et.al, (2022) showed a different result, where obese diabetic mellitus patients have a 1.60 times greater risk (95% CI: 0.93 – 2.76) of experiencing CKD-DM compared to those who are not obese.[25] There are various studies related to obesity and CKD-DM with varying results. Some show that BMI is not related to CKD-DM. Others show that obesity or high BMI is a risk factor for CKD-DM, while some

other studies suggest that a high BMI is a protective factor against CKD-DM. Potential reasons for the differing research results may include different study participants. A negative correlation between BMI and CKD-DM, where a higher BMI leads to a lower risk of CKD-DM, is widely observed in Asia. Therefore, the potential factor influencing the Adjusted PR value of this study is due to the research being conducted in Indonesia one of the Asian countries.[26]

The limitation of this study relates to the secondary data sources used, in which there is a potential for loss or incompleteness of data. Additionally, the scope of variables available in secondary data sources may only partially capture some relevant factors influencing the phenomenon under investigation. Future research should consider employing primary data collection methods to address these limitations comprehensively.

CONCLUSION AND RECOMMENDATION

The prevalence of CKD-DM in Indonesia is 18 per 1,000 population. Risk factors for CKD-DM in Indonesia include pre-elderly age, gender, hypertension, smoking, and lack of exercise. Gender is the dominant factor of CKD-DM in Indonesia. The differential hormonal environment between gender plays a significant role in the pathophysiology of CKD. Higher testosterone levels in men may lead to increased kidney damage and a faster decline in kidney function. Understanding the gender-related differences in CKD is crucial for tailoring prevention strategies and treatment plans. It is desired that healthcare providers and program makers should recognize gender differences in the progression of CKD and conduct screening program for risk factors of CKD-DM such as blood tests (e.g., eGFR) and urine tests (e.g., urine albumin-to-creatinine ratio).

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AUTHOR CONTRIBUTIONS

ASAZ Sand CS contributed to the conceptualization of the research; ASAZ collected and analyzed the data; ASAZ wrote the script; The manuscript and data analysis were evaluated by CS. The manuscript's published version has been approved by all authors, who have also reviewed and approved it. The authors read and approved the final manuscript. ASAZ = Asy Syifa Anwari Zahra; CS = Chandrayani Simanjorang.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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