

## RELATIONSHIP BETWEEN TREATMENT ADHERENCE AND PROGRESSION OF DIABETIC NEPHROPATHY

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Masuk: 03-06-2020, revisi: 14-10-2020, diterima untuk diterbitkan: 18-03-2021

### ABSTRAK

Perhimpunan Nefrologi Indonesia (Pernefri) tahun 2006 merilis data penderita gagal ginjal kronis di Indonesia sebesar 12,5%. Etiologi terbesar gagal ginjal kronis menurut Indonesian Renal Registry tahun 2018 adalah penyakit ginjal hipertensi sebesar 39% dan nefropati diabetik sebesar 22%. Potong lintang pada pasien di RS"RT" Jakarta tahun 2018-2019. Variabel bebas dalam penelitian ini adalah komorbid hipertensi dan kepatuhan berobat, sedangkan variabel terikat dalam penelitian ini berupa kategori risiko progresifitas perburukan ginjal serta hubungan sebab akibat diuji dengan *Pearson Chi Square* dan uji alternatif *Fisher Exact Test*. Penelitian berlangsung mengikutsertakan 26 responden, dengan prevalensi hipertensi pada pasien nefropati diabetik sebesar 17 (65,4%). Delapan puluh persen responden yang tidak rutin berobat pada kelompok hipertensi memiliki progresifitas penyakit gagal ginjal hingga kategori Deep Red (Highest Risk). Analisa uji statistik *Fisher Exact* pada kelompok dengan riwayat penyakit penyerta berupa hipertensi didapatkan tidak hubungan yang bermakna antara tidak rutin berobat dengan progresifitas penyakit gagal ginjal kronis kategori Highest-Very Highest Risk ( $p\text{-value} = 0,515$ ) tetapi secara besar risiko didapatkan bahwa kelompok yang tidak rutin berobat memiliki risiko 1,33 (0,962 – 1,848) kali untuk memiliki progresifitas penyakit gagal ginjal kronis kategori Highest-Very Highest Risk. Dapat disimpulkan bahwa engontrol tekanan darah dan rutinitas berobat dapat memperlambat perburukan fungsi ginjal akibat komplikasi lanjut dari nefropati diabetikum, walaupun belum didapatkan hubungan yang bermakna dikarenakan kurangnya besar sampel pada penelitian ini.

**Kata Kunci:** nefropati diabetes; hipertensi ; prognosis

### ABSTRACT

In 2006, the Indonesian Renal Registry (Pernefri) shows about 12,5% of people in Indonesia suffer from chronic kidney disease. The most common cause of chronic kidney disease in 2018 in Indonesia is 39% by renal hypertension and 22% by Diabetic Nephropathy. This cross-sectional study was conducted at "RT" Hospital in Jakarta from 2018 to 2019. The Independent variable in this research was comorbid hypertension and obedience treatment, whereas dependent variables were risk category for kidney deterioration progression and the causal relationship tested with *Pearson Chi-Square* and *Fisher exact* as an alternative test. The study included 26 respondents, with 17 (65.4%) patients having hypertension in diabetic nephropathy. Eighty percent of respondents who did not routinely seek treatment in the hypertension group had progression from kidney failure to the Deep Red (Highest Risk) category. Fisher Exact statistical test analysis in the group with a history of comorbidities in the form of hypertension found no significant relationship between non-routine treatment with the progression of chronic kidney failure in the Highest-Very Highest Risk category ( $p\text{-value} = 0.515$ ). Still, a large risk was found in the non-group routine treatment with a chance of 1.33 (0.962 - 1.848) times to have the progression of chronic kidney failure in the category of Highest-Very Highest Risk. Can be concluded that controlling blood pressure and treatment proven to slow worsening kidney function in nephropathy diabetic, even though no significant relationship has been found due to lack of sample.

**Keywords:** diabetic nephropathy; hypertension; prognosis

# 1. INTRODUCTION

## Background

The kidney filtrates about 120-150 liter of blood and produces 1-2 liter urine daily. The kidney has about 1 million filtration units called a nephron. A nephron consists of glomerulus and tubules; the glomerulus function is to filtrate plasma and other waste and prevent the loss of red blood cells and large molecules like protein. The tubule function is to reabsorb the substance selectively need for the body and secrete others back to the lumen.(Basile et al., 2012; Meltzer, 2018; Palmer & Clegg, 2019) The kidney also produces enzymes such as renin to regulate natrium and blood pressure, and erythropoietin hormone that stimulates the bone marrow to produce red blood cells and regulate active form vitamin D that is needed for bone. (Kemenkes RI, 2017)

Kidney disease is divided into two forms, acute renal failure, and chronic kidney disease. Chronic kidney disease is a condition where the kidney cannot filtrate blood normally that impacts fluid excess in the body, interfering with the patient's health (Kemenkes RI, 2017; Webster et al., 2017). National Chronic Kidney Disease Fact Sheet in 2017 release the fact that 30 million people, or 15% of the adult population in the United States of America, have chronic kidney disease. Ironically, most of them were diagnosed when they already have an impaired renal function, and 48% of them never had hemodialysis and didn't aware of progressivity worsening renal function. On the other side, 96% of people diagnosed with low and moderate declining kidney function weren't aware of chronic kidney disease. (Centers for Disease Control and Prevention, 2017)

According to Chronic Kidney Disease in the United States in 2019, the risk factor for chronic kidney disease is age above 65 (38%), female gender (15%), and black non-Hispanic race (16%). The chronic illnesses that cause CKD are diabetes, 38%, and hypertension, with 26%. Other causes of CKD are heart disease, obesity, genetics, infection, and trauma (CDC, 2019). Riset Kesehatan Dasar (Riskesdas) in 2013 release data that 0,2% population were diagnosed with chronic kidney disease since age 15. This number is lower than other prevalence of chronic kidney diseases in other countries. Indonesia Renal Registry (Pernefri) in 2016 found that 12,5% total population had CKD. (Badan Penelitian dan Pengembangan Kesehatan, 2013; Kemenkes RI, 2017) The most common etiology CKD in 2018 from the Indonesian Renal Registry was renal hypertension, about 39%, and diabetic nephropathy 22%. It also implies in the last stage CKD, 36% by hypertension, and 28% in diabetic nephropathy (PPERNEFRI, 2016).

In general, diabetic nephropathy is defined as a clinical syndrome in diabetes mellitus patients characterized by persistent albuminuria (> 300 mg / 24 hours) at least two examinations over 3 to 6 months. In America and Europe, diabetic nephropathy is the leading cause of terminal renal failure. The incidence of diabetic nephropathy in type 1 and type 2 diabetes is comparable. The incidence in type 2 is often greater than in type 1 because the number of patients with type 2 diabetes mellitus is more than type 1 diabetes mellitus. In America, diabetic nephropathy is one of the leading causes of death. among all complications of diabetes mellitus, and the most common cause of death is due to cardiovascular complications (Sudoyo, 2016).

Hyperfiltration is still considered to be the beginning of a pathogenic mechanism in the rate of kidney damage. Research by Brenner et al. Shows that when the number of nephrons is decreased continuously, glomerular filtration of healthy nephrons will increase as a form of compensation. Hyperfiltration that occurs in the remaining healthy nephrons will gradually lead to sclerosis of the nephrons. The mechanism for this increased glomerular filtration rate in

diabetic nephropathy is still clearly correct. It is probably due to afferent arterioles' dilatation by a glucose-dependent effect chained by vasoactive hormones, IGF-1, Nitric Oxide, prostaglandins, and glucagon. The direct result of hyperglycemia is the stimulation of cell hypertrophy, synthesis of the extracellular matrix, and the production of TGF- $\beta$ , which is chaired by the activation of protein kinase-C (PKC), which is included in serine-threonine kinase which has vascular functions such as contractility, blood flow, cell proliferation, and capillary permeability. Hypertension that occurs together with increased kidney damage will also encourage sclerosis in the kidneys of diabetic patients. Studies in diabetic animals have shown vasoconstriction of arterioles due to abnormalities in the renin/angiotensin system. It is thought that hypertension in diabetes is mainly due to intrarenal or intraglomerular efferent arteriolar spasm (Sudoyo, 2016).

One way to reduce disease progressivity is to control hypertension and blood sugar. Previous research from Wijaya et al. explained that one of the interventions that are considered effective in controlling blood sugar and blood pressure is to increase medication adherence. (Wijaya et al., 2020) And it is also necessary to manage various risk factors for uncontrolled hypertension and diabetes, such as a balanced diet, exercise, adequate sleep, and others (Firmansyah & Luciana Prawiro, 2020).

This problem becomes special because hypertension in patients with type 2 diabetes mellitus will accelerate renal function decline. This study aims to see the comparison between risk groups for kidney failure diabetic nephropathy patients with comorbid hypertension and medication adherence.

## **2. METODE**

We used an observational analysis with a cross-sectional conducted in "RT" Hospital from Jarunari until May 2019. The subject was obtained from a diabetic nephropathy patient in "RT" Hospital from 2018-2019 who met the inclusion criteria. The inclusion criteria were patients with type 2 diabetes Mellitus and had kidney complications (hypertension, diabetes, and end-stage chronic kidney disease). Diagnosis of diabetic nephropathy is by looking at medical records and laboratory examinations written in medical records. The estimated sample was 102 samples using non-random consecutive sampling. The exclusion criteria were patients with uremic syndrome, nephrotic syndrome, sepsis, urinary tract infection, post-infection streptococcus glomerulonephritis, type 1 diabetes mellitus, and gestational diabetes. The independent variable was obedience treatment or controlled hypertension and a history of hypertension. The dependent variable was the group with the risk of kidney failure in a patient with diabetic nephropathy. The result then analyzes with Pearson Chi-square with an alternative test, Fisher Exact test, to see the significant value between 2 groups. This research got permission from the Faculty of Medicine at Tarumanagara University.

## **3. RESULTS AND DISCUSSION**

From 26 responden, 11 males (42,3%), 15 females (57,7%), and 17 (65,4%) of them had hypertension in diabetic nephropathy. Average weight, height, and body mass index were 64,15 (11,34) kg, 162,58 (9,29) cm, and 23,81 (3,27) kg/m<sup>2</sup>. Obesity prevalence in our subject was 12 patients (46,2%). Average albumin, HbA1c, random plasma glucose, fasting plasma glucose, ureum, and creatinine were 2,91 (0,54) g/dL; 7,82 (1,81) %; 210,19 (53,56) mg/dL; 144,77 (36,49) mg/dL; 111,73 (69,15) mg/dL; 3,55 (2,54) mg/dL. Glomerular filtration rate was 23,87 (14,86%) with progression from Deep Red (Highest Risk) 11 (42,3%) respondent, Red (Very

High Risk) 8 (30,8%) respondent, Orange (High Risk) 6 (23,1%) respondent, and Yellow (Moderately Increase Risk) 1 (3,8%) respondent.

Table 1. Characteristics of Diabetic Nephropathy Patients in "RT" Hospital from 2018 to 2019

Parameter	N (%)	Mean (SD)	Med (Min-Max)
Age		69 (9,65)	68,5 (50 – 84)
<b>Gender</b>			
• Male	11 (42,3%)		
• Female	15 (57,7%)		
<b>Ever had hypertension</b>			
• Yes	17 (65,4%)		
• No	9 (34,6%)		
Weight		64,15 (11,34)	61 (49 – 94)
High		162,58 (9,29)	162 (147 – 182_
BMI		23,81 (3,27)	24 (17 -30)
<b>Nutritional Status</b>			
• Obesity	12 (46,2%)		
• Overweight	6 (23,1%)		
• Normal	7 (26,9%)		
• Underweight	1 (3,8%)		
Albumin		2,91 (0,54)	2,9 (1,7 – 4,0)
HbA1c		7,82 (1,81)	7,4 (5,3 – 14,0)
Random blood glucose		210,19 (53,56)	207 (118-354)
Fasting blood glucose		144,77 (36,49)	141,5 (52 – 254)
Ureum level		111,73 (69,15)	93 (32 – 296)
Creatinine level		3,55 (2,54)	2,60 (1,14 – 10,73)
History Treatment			
Glomerular Filtration Rate		23,87 (14,86)	20,75 (4,00 – 55,40)
<b>Progressivity Risk</b>			
• Deep Red (Highest Risk)	11 (42,3%)		
• Red (Very High Risk)	8 (30,8%)		
• Orange (High Risk)	6 (23,1%)		
• Yellow (Moderately Increased Risk)	1 (3,8%)		
• Green (Low Risk)	-		

All respondents were divided into two groups, patients with hypertension and without hypertension. Each group is divided into two groups, routine treatment /control with not routine treatment / uncontrolled and chronic kidney failure progression. Seventeen patients had hypertension, 12 were regular to control, and five patients didn't control regularly. Eighty percent responded that hypertension and not routinely treated had progression in renal failure up to Deep Red (Highest Risk). The difference was seen in a patient who had hypertension but was controlled; only 50% had progressivity risk renal failure to Deep Red (Highest Risk). The number goes drastically low with the patient who hadn't had hypertension. None of them reach Deep Red (Highest Risk) category in the group that hadn't had hypertension and routine medical treatment, and only 16,7% chance person to had Deep Red (Highest Risk) category for the group that hadn't had hypertension and not routine seek medical treatment.

Table 2. Distribution of Hypertension History to Diabetic Nephropathy Patient Treatment History

History of Hypertension	History of Therapy	Prognosis of CKD by GFR and Albuminuria Category			
		Deep Red (Highest Risk)	Red (Very High Risk)	Orange (High Risk)	Yellow Moderately Increased Risk)
YES	Not routine / not controlled	6 (50%)	3 (25%)	3 (25%)	-
	Routine / Controlled	4 (80%)	1 (20%)	-	-
NO	Not routine / not controlled	-	2 (66,7%)	1 (33,3%)	-
	Routine / Controlled	1 (16,7%)	2 (33,3%)	2 (33,3%)	1 (16,7%)

There is no relation in the hypertension group between not routinely treated and chronic renal failure progressivity (Highest-Very Highest Risk category) in Fisher Exact analytical study (p-value = 0.515). Still, in general, the respondent who didn't get treatment routinely had a chance of 1.33 (0.962 - 1.848) progression time to renal failure up to the Highest - Very Highest Risk Category. This was seen with 95% Confidence Interval, and the result was not strong enough because of the lack of samples.

Table 3. Comparison of Kidney Failure Risk Groups for Diabetic Nephropathy with Comorbid Hypertension and Treatment Compliance

History of Hypertension	History of Therapy	Prognosis of CKD by GFR and Albuminuria Category		PR	Confidence Interval		p-value
		Highest -Very High Risk	High Risk		Lower	Upper	
YES	Not routine / not controlled	5 (100%)	-	1,333	0,962	1,848	0,515
	Routine / Controlled	9 (75%)	3 (25%)				
NO	Not routine / not controlled	3 (50%)	3 (50%)	0,750	0,242	2,325	1,000
	Routine / Controlled	2 (66,7%)	1 (33,3%)				

This study does not discuss how long it takes diabetes mellitus to fall into a state of kidney failure. In tracing the previous literature, it is known that there is 5 stage in diabetic nephropathy, first is where there is an elevation in GFR up to 40% above normal level and occur in 0-5 years after someone got diagnose. (Pratama, 2013; Rivandi & Yonata, 2015; Utara & Utara, 2013) In the first stage, diabetic tubulopathy occurs based on the structural and functional change in hypertrophy cuboidal epithelial, thickening glomerular base membrane, mesenchymal-epithelial transition, and accumulation of glycogen. Glomerular hypertrophy was diffuse and global and increased total volume and capillary size in renal, but albumin excretion still normal. Still, the loss can occur if the patient had bad control of their metabolic, fever, over-exercise, and stress.

The second stage is the Silent Stage, which takes place about 5-10 years after diagnosed. In this stage, microalbuminuria occurred, where albumin excretion around 30-300 mg/24 hours. (Giacco & Brownlee, 2010) and GFR getting higher, and the metabolic got worse. The third stage was Incipient Diabetic Nephropathy that last 10-15 years after got diagnose. Histopathology, shown a thickening glomerular base membrane. In this stage, there is an increase in blood pressure and high GFR still. Controlling hypertension and blood glucose prevents it from getting worse. The fourth stage was nephropathy diabetes has manifest clinically and decreasing GFR below normal. This stage takes place 15-20 years after someone got diagnose. Complications from diabetes like retinopathy and neuropathy can occur, and the choice treatment was monitor blood glucose and hypertension. Last stage was renal failure that marked by low GFR and uremic syndrome. In this stage kidney transplantation was the option. (Giacco & Brownlee, 2010; Micahl & Thorp, 2012; Pratama, 2013; Rivandi & Yonata, 2015; Utara & Utara, 2013)

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Figure 1. Prognosis of CKD by GFR and Albuminuria Category (Khwaja, 2012)

In this study, the mean random blood glucose in diabetic nephropathy patients was 210.19 (53.56) mg / dL, or in other words, generally, respondents had uncontrolled random blood glucose levels. On the other hand, many people with diabetes nephropathy also experienced hypertension, namely in 65.4% of respondents. High blood pressure has been seen in 50% of patients with uncontrolled high blood glucose. Hypertension in type 1 diabetes mellitus will increase microalbuminuria and kidney damage. A cross-sectional study in Denmark with 1.750 patients with diabetes and 12.000 case-control showed no difference in micro and macroalbuminemia between 2 groups, and no difference in hypertension incidence rate between type 1 diabetes mellitus and the general population (3,9% vs. 4,4%). (Nørgaard et al., 1990) A study from Lurbe shows no difference in the incidence of hypertension and micro-macroalbuminuria between type 1 diabetes mellitus and the general population. Lurbe concludes that there is a relation between age, hereditary, and kidney function. Kidney function and kidney leakage incidence are lower in the younger generation, with or without type 1 diabetes mellitus. (Nazar, 2014).

This study also reported that 46.2% of respondents were obese, and 65.4% had hypertension during diabetes nephropathy. Patients with type 2 diabetes mellitus usually have comorbid hypertension before got renal failure. This happened because of obesity and overweight contribute to glucose intolerance or hypertension. Other studies have also shown that the prevalence of hypertension in type 2 DM had proteinuria about 30-42%. This study clarifies that type 2 DM has a relation more to decrease GFR rather than hypertension. But there is another study that said hypertension play a role in renal failure and cardiovascular disease (Murea et al., 2012; Nazar, 2014)

This study shows that generally, respondents have albumin levels at the threshold, namely 2.91 (0.54), high levels of urea and creatinine, namely 111.73 (69.15) and 3.55 (2.54). Other research shows that microalbuminuria is the main symptom of hypertension in both types of diabetes and decreased GFR that decreases cardiovascular function. (Inker et al., 2011; MacIsaac & Jerums, 2011; Mangray & Vella, 2011; Moody et al., 2016) Diabetic nephropathy has higher progressivity; up to 90% get renal failure. This has happened because of many factors, blood glucose level, blood pressure, fat, and other) and also patient hemodynamics. Hereditary and genetic are also important determinants progress of the disease. (Nazar, 2014).

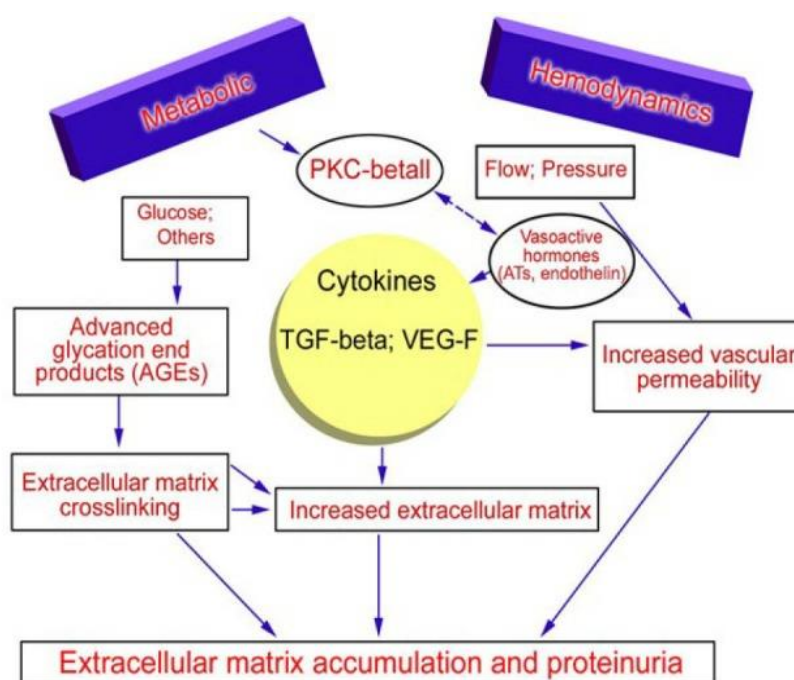
Pathogenesis of diabetic nephropathy so complex that it starts from renal apparatus up to whole kidney damage. Hyperglycemia is the main cause of kidney dysfunction; it causes glomerular hyperfiltration and endothelial dysfunction. Both of this condition change the glomerular base membrane, that sign first was hypertrophy intraglomerular cell. Other changes that happen are nodular intercapillary glomerulosclerosis and change glomerulus matrix. Albuminuria is the first sign of renal damage (9). Renal anatomy shift occurred because of volume expansion and hypertension, causing increased sodium reabsorption in the renal tubule. One of the proximal tubule functions to take protein triggers cascade inflammation that makes inflammation and fibrosis in interstitial tubules (Navarro-González et al., 2011; Nazar, 2014).

Renin-Angiotensin-Aldosterone System (RAAS) in type 2 diabetes mellitus contributes to significant diabetic nephropathy severity. RAAS function is to regulate systemic, glomerulus blood pressure and Sodium reabsorption by angiotensin II and in the pro-fibrotic stage by aldosterone. Glycated protein occurs in renal cells, caused by long periods of uncontrolled blood sugar levels are considered important in diabetic nephropathy and other microvascular complications. Uncontrolled blood sugar related to amino acid and protein non-enzyme-reaction produces Advanced Glycation End Products (AGEs). AGEs are stable compounds and long-lasting in circulation and stored in many tissues, including the kidney. AGEs and their target receptors interaction triggers cascade inflammation that contributes to endothelial dysfunction. All inventions are shown that AGEs are related to hyperglycemia and metabolism, inflammation processes, and oxidative stress. AGEs accumulation was crowned as an early predictor for diabetes kidney complications. (Nazar, 2014).

One of the effective ways to inhibit the progress of diabetic nephropathy is to control blood glucose. Blood glucose control can be done by various methods, starting from education, teaching aids, and routine monitoring. (Wijaya et al., 2020) Controlling blood pressure in early-stage type 2 diabetes mellitus will slow the progress of diabetic nephropathy. Its prolonged hypertension contributes to endothelial kidney injury. Research has shown that lowering blood

pressure in patients with type 2 diabetes is a strong intervention to prevent complications (Fioretto et al., 2014; Nazar, 2014).

The pathogenesis of diabetic nephropathy can summarize into three different mechanisms. (1) The expansion mesangial membrane is caused by hyperglycemia that impacts the formation of glycated protein. (2) coagulation glomerular cell is because by prolonged inflammation. (3) expansion of afferent renal artery or ischemia in a constricted vessel in apparatus glomerulus because of hialin deposition (Lerma & Batuman, 2014; Nazar, 2014). Summary of pathogenesis diabetic nephropathy serves in picture 1.



**Figure 2. Pathogenesis of Diabetic Nephropathy** (Nazar, 2014)

#### 4. CONCLUSION AND SUGGESTION

##### Conclusion

Controlling blood pressure and glucose are major factors to prevent decreased renal function in diabetic nephropathy and increase life expectancy. Even though there is significant relation between not routinely treatment and progression renal failure Highest-Very Highest Risk category (p-value = 0,515), but there is a risk 1,33 (0,962 – 1,848) time progress to renal failure up to the Highest-Very Highest risk category in the group who didn't routinely get treatment. This statistical significance applies to groups with and without a history of hypertension, but clinically high blood pressure is one factor that influences the deterioration of kidney function.

##### Suggestion

We recommend to research with a larger sample and conducted at several other dialysis centers in Jakarta.



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