

Potential Risk Factors for Mortality Due to Cardiovascular Disease Among Hemodialysed Patients in Indonesia

Diana Laila Ramatillah^{1*}, Syed Azhar Syed Sulaiman², Kashif Ullah Khan³

¹Pharmacy Faculty, Universitas 17 Agustus 1945 Jakarta, Indonesia

²Director AMDI-USM sains@Bertam, Penang, Malaysia

³Department of Clinical Pharmacy, College of Pharmacy, University of Hail, Saudi Arabia

ABSTRACT

Severe vascular calcifications, alterations in cardiovascular structure and function, immune dysfunction, and anemia are adverse effects of parathyroid hormone (PTH), which may contribute to increase risk factors of cardiovascular morbidity and mortality among renal failure patients. To evaluate the potential risk factors for mortality due to cardiovascular disease among hemodialysed patients in Indonesia, this cohort study was conducted. This study included 178 patients on hemodialysis who had been followed up two times a week for nine months (prospective cohort) and 185 patients who died in the last five years (retrospective cohort). Universal sampling technique were used to select the study subjects. Male was prevalence among hemodialysed patients in hemodialysis center, Jakarta, Indonesia and the third group of age (51-60 years) was predominant among these patients. Java ethnicity was found in almost 50% hemodialysed patients in this hemodialysis center. Most of those patients had hypertensive family history. Besides that, more than 70 percent of them were married and non-smoker. The study found that cardiovascular disease caused mortality among hemodialysed patients in Indonesia and the duration of cardiovascular disease influenced the probability of death/risk of mortality among these patients (HR 2.39, $p = 0.006$). Mortality among patients on hemodialysis in this study was caused by cardiovascular disease, and this cause of death was included in one of the biggest causes. During the study, several practice patterns revealed no PTH level check, no patients got calcimimetic agents such as rocalcitriol/calcitriol and calcium value check was conducted irregularly. As we know, there is a correlation between PTH, calcium and cardiovascular disease. Hence, mortality due to cardiovascular disease among hemodialysed patients significantly correlated with the duration of cardiovascular disease, and potentially with lack of PTH check, calcium check and rocalcitriol/calcitriol supplement given to those patients.

Keywords: Secondary hyperparathyroidism; mortality; patients on hemodialysis; Indonesia

ARTICLE HISTORY

Received: February 2019

Revised: December 2019

Accepted: August 2020

*corresponding author

Email: dianalailaramatillah@gmail.com

INTRODUCTION

Diabetic and hypertensive are the main diseases which cause hemodialysis among end-stage renal disease patients (Indonesian Renal Registry, 2014). Hemodialysis is one of the treatment in replacing renal function for end-stage renal disease/chronic renal insufficiency (CRI) patients (National Kidney Foundation, 2013). Abnormalities in acid-base and vitamin D-parathyroid hormone (PTH) homeostasis as a result of reduced bone mineral density (BMD) may also occur among CRI patients (Nikodimopoulou & Liakos, 2011). Many patients with mild to moderate CRI also have decreased serum 1,25-(OH)₂ vitamin D and increased PTH levels (3), and their bone biopsies show evidence of PTH excess and increased bone turnover (Malluche et al., 1976). The chronic elevation of PTH, as in CRF, has been (Chronic Renal Failure) shown to cause a sustained elevation in the calcium of hepatocytes (Greten et al., 1996). For patients who had a renal problem like chronic kidney disease will have problems in calcium and phosphorus metabolism (Moe et al., 2007). To prevent this condition, numerous drugs, including phosphorus

binders, vitamin D compounds, and calcimimetic agents, have been specifically developed and promoted (Hayen et al., 2017).

Nephrology guidelines recommend targets and treatment strategies to correct serum levels of phosphorus, calcium, and parathyroid hormone because observational data suggest there is an association between these potential risk biomarkers and vascular disease and death (Hayen et al., 2017; National Kidney Foundation, 2003; Flanc et al., 2000). On the other hand, based on the preliminary study, checking laboratory value of calcium was irregular among hemodialysed patients in Indonesia. No data were found about parathyroid hormone level and parathyroidectomy. Besides that, most of these patients were given calcium carbonate instead of calcimimetic agents such as calcitriol. Cardiovascular disease contributed as a cause of mortality among these patients. Because of these reasons, evaluation of potential risk factors for mortality due to cardiovascular disease among hemodialysed patients in Indonesia is important to be conducted.

Table 1. Sociodemographic data of hemodialysed patients

Characteristics	Followed up for nine months (n=178) n (%)	Had died since last five years (n=185) n (%)
Gender		
Male	106 (59.60)	118 (63.80)
Female	72 (40.40)	67 (36.20)
Age (years)		
≤ 40	21 (11.80)	13 (7.00)
41-50	37 (20.80)	27 (14.60)
51-60	57 (32.00)	70 (37.80)
61-70	45 (25.30)	57 (30.80)
>70	18 (10.10)	18 (9.70)
Ethnic		
Chinese (Indo)	1 (0.6)	-
Aceh	1 (0.6)	-
Batak	4 (2.2)	-
Minang	25 (14)	-
Melayu	3 (1.7)	-
Jambi	1 (0.6)	-
Palembang	4 (2.2)	-
Betawi	21 (11.8)	-
Sunda	32 (18)	-
Java	83 (46.6)	-
Bali	1 (0.6)	-
Sulawesi	1 (0.6)	-
Others	1 (0.6)	-
Malay	0	0
Chinese (Malay)	0	0
Indian (Malay)	0	0
Family history		
Diabetes Mellitus	46 (25.80)	-
Hypertensive	62 (34.80)	-
Diabetes Mellitus & Hypertensive	37 (20.50)	-
Unknown	33 (18.50)	-
No	0	-
Smoking		
Smoker	3 (1.70)	-
Non-Smoker	175 (98.30)	-
Marital status		
Single	36 (20.20)	-
Married	142 (79.80)	-

Increasing mortality is a big issue among hemodialysed patients (Indonesian Renal Registry, 2014). Finding the risk factors of mortality may help to decrease the mortality cases. The study conducted in less than one year following patients in the ward will have a lack of mortality data. Hence, look to the retrospective data is important to find the risk factor of mortality among these patients.

MATERIAL AND METHODS

Study Location

Current research study was carried out in the hemodialysis ward of Cempaka Putih Islamic Hospital, center Jakarta, Indonesia.

Study Participants

The study included diabetic and/or hypertensive patients who undergo hemodialysis. Universal sampling was used to select 178 patients who had been followed for nine months, 2-3 times in a week, and 185 patients who died in the last five years in a hemodialysis center Cempaka Putih Islamic Hospital Jakarta, Indonesia.

Study Design

A combination of cohort prospective and retrospective study was conducted in this hemodialysis center. Inclusion criteria for this study are All hemodialysis patients who have diabetic and/or hypertensive and hemodialysed patients with age 18 years old above. For exclusion criteria in this study are hemodialysed patients

with cancer, pregnancy, HIV/AIDS and Systemic Lupus Erythematosus.

Ethical Clearance

Ethical clearance was sourced by the medical committee from the Faculty of Medicine Indonesia. The approval letter was given before starting of data collection with the number: 728/UN2.F1/ETIK/2015.

Data Collection and Handling

The researcher would define the patients by the list of patients in the ward. Before collecting data from medical record, the researcher would explain the research (background and the purpose of the research) to the patients. Data collection would be starting after patients signed the informed consent as an agreement of the research. The data were arranged according to socio-demography status, laboratory value checked, and current medication and transferred to clinical research form (CRF). The researcher would follow-up the patients for nine months, 2-3 times a week, to see the progress of these patients who were written in their medical record, including their laboratory results.

RESULTS AND DISCUSSION

There were two types of data that had been collected from the hemodialysis center; retrospective and prospective. Retrospective sample was done by taking

data of hemodialysis patients who had died last five years and prospective sample was collected by following and evaluating hemodialysis patients for 9 months.

In this study, there are six characteristics of demographic data among diabetic and/or hypertensive patients who undergone hemodialysis in hemodialysis center Jakarta, Indonesia; gender, age, ethnic, family history, smoking and marital status. There are five groups of age in this study (≤ 40 , 41-50, 51-60, 61-70, and > 70 years). The age distribution shows that most patients who had been followed up for nine months (32%) were aged 51-60 years. This age group constitutes the majority among Indonesian patients who had died during the last five years.

Java represents 46.6% of the ethnic in Indonesia. For family history, hypertensive was the highest in the number of hemodialysed patients for patients who had been followed up for 9 months. Almost all patients were married, non-smokers, and un-employed, as shown in Table 1.

Thyroidectomy is done if the parathyroid hormone is high. For hemodialysis center in Jakarta, Indonesia, checking of parathyroid hormone had not been done. Because of that, no report about thyroidectomy among hemodialysed patients in this hemodialysis center as shown in Table 2.

Table 2. Practice pattern among hemodialysed patients

No	Practice Pattern	Followed up for nine months (n=178)	Had died since last five years (n=185)
1	Hyperparathyroidism check	None	None
2	Thyroidectomy surgery	None	None
3	Supplement to prevent from bone mineral density problem (rocalcitriol/calcitriol supplement)/calcimimetic agents	None = 178 Yes = 0	None = 185 Yes = 0
4	Calcium carbonate	Yes	Yes
5	Calcium level checked	Irregular	Irregular

Table 3. The number of hemodialysed patients who diagnosed heart disease based on ESRD being diagnosed among nine months followed-up of hemodialysed patients

Component	ESRD being diagnosed (years ago)			Total
	≤ 5 years	$>5-10$ years	$>10-15$ years	
Heart disease being-diagnosed (years ago)				
Never	112	15	4	131
≤ 5 years	37	3	1	41
> 5 years	4	2	0	6
Total	153	20	5	178

Table 4. Prevalence of mortality based on cause of death among hemodialysed patients

Cause of ESRD	CVD		Sepsis		C		GI		Others (Accident)		Unknown	
	Pr	R	Pr	R	Pr	R	Pr	R	Pr	R	Pr	R
DM	-	-	-	-	-	-	-	-	-	-	-	-
HT	11	15	1	20	-	4	-	5	-	9	-	61
DM&HT	3	7	2	13	-	6	-	2	-	5	-	38
Total sample	14	22	3	33	-	10	-	7	-	14	-	99
HD (Pr+R)	36		36		10		7		14		99	

DM, Diabetic; HT, Hypertensive; CVD, Cardiovascular Disease; C, Cerebrovascular; Pr, Prospective/hemodialyzed patients who had been followed up for 9 months; GI, Gastro Intestinal; R, Retrospective/hemodialyzed patients who had died since last 5 years

Table 5. Potential risk factors of probability of dying among hemodialysed patients

Potential Risk Factors	B	Exp (B) Hazard Ratio	95% CI For Exp (B)	p Value
Duration of Cardiovascular disease	0.87	2.39	1.29-4.43	0.006 ^a
Heart Disease	-0.98	0.38	0.03-2.74	0.04

^aCox Regression

During the study, it was known that no patients received another supplement (calcimimetic agents) such as rocalcitriol or calcitriol except calcium carbonate to prevent bone mineral density problem in hemodialysis center Jakarta, Indonesia. Calcium level among those patients was not checked regularly. In hemodialysis center Jakarta, Indonesia, 41 of 47 patients were diagnosed with heart disease with these patients for less than 5 years and 153 patients on hemodialysis had been diagnosed with ESRD for less than 5 years in Table 3. From the table, no patient was found in the category patients who had been diagnosed ESRD > 10-15 years and having heart disease > 5 years.

There were six categories of mortality causes among hemodialysed patients in this study including cardiovascular disease, sepsis, cerebrovascular, gastro intestinal, accident and unknown as shown in Table 4. Cardiovascular disease and sepsis are the causes of mortality, with the highest number of patients for both groups of patients (had been followed up for nine months and died since the last five years); 36 patients died with cardiovascular disease, and 36 patients died with sepsis. However, for patients who died in the last five years, 99 of 185 patients did not know the cause of death. During followed up for nine months, only cardiovascular and sepsis were noticed as causes.

Duration of having cardiovascular disease elevated risk of death more than two times during follow up of 9 months hemodialysis and described a significant relationship with the probability of dying (HR 2.39, $p = 0.006$), while for heart disease showed a negative association with the probability of dying (HR = 0.38, $p = 0.04$) as shown in Table 5.

According to Indonesian Renal Registry 2014, there were more male (> 50 %) undergoing hemodialysis with majority over the age of 50 and hemodialysis was more common among the Java ethnic group (Indonesian Renal Registry, 2014). This report supports our findings.

Family history, smoking status, and marital status are part of sociodemographic, which are necessary to be known. From our findings, family history of hypertensive contributed to the highest number of hemodialysed patients, and this finding was supported by Almeida et al., 2015 study. At the same time, they found that hypertension and type 2 diabetes mellitus are responsible for more than 50 % of end-stage renal disease (Almeida et.al, 2015). In terms of smoking status among hemodialysed patients, smoking is not a significant risk factor for renal failure (Hallan & Orth, 2011). Venícios et al. (2017) study showed more than 50 % hemodialysed patients had partners (married). These findings were similar to our finding, while most of hemodialysed patients were non-smoking and married.

From the study, it was found that cardiovascular disease and sepsis caused mortality among hemodialysed patients in Indonesia, and the duration of cardiovascular disease influenced the probability of dying/risk of mortality among these patients. During the study, few practice patterns revealed no parathyroid hormone level check, and it caused no thyroidectomy surgery among those patients. Besides that, no patients got calcimimetic agents, and calcium value check was conducted irregularly, only when patients needed it.

Parathyroid hormone and calcium level should be monitored regularly in patients on hemodialysis. As we know, patients on hemodialysis are patients with chronic renal problem. This condition will make the insufficiency of calcium in this patient's body. If these patients did not get proper medication related to calcimimetic agents, the Parathyroid Hormone (PTH) would be high to make the calcium balance in the patient's body (National Kidney Foundation, 2009).

Increased myocardial calcium was positively associated with an increase in CaxP (Calcium-Phosphorus Product) and inversely associated with LVEF (Left Ventricular Ejection Fraction) (Block & Port, 2000). The risk associated with elevated serum phosphorus has focused on its impact on renal osteodystrophy. A growing body of evidence, however, suggests the abnormalities in serum phosphorus and CaxP. More recent data have consistently shown a high rate of valvular calcification in ESRD patients (Block & Port, 2000). Calcification of large arteries, valves, and atherosclerotic plaques may occur in a somewhat different fashion and in these situations, membrane vesicles that are exocytosed from aging or damaged smooth muscle cells within the lipid-rich atherosclerotic plaque can serve as the initial site of apatite deposition (Block & Port, 2000). Parathyroid hormone (PTH) may contribute to cardiovascular morbidity and mortality in several additional ways, including a permissive role in arteriolar wall thickening and myocardial interstitial fibrosis, promoting an increase in triglycerides and low density lipoprotein (LDL) cholesterol levels, and by contributing to hypertension (Block & Port, 2000). Santhi et al. found strong relationships between elevated serum phosphate, calcium-phosphate product, and parathyroid hormone and cardiac causes of death in hemodialysis (HD) patients, especially deaths resulting from CAD and sudden death (Ganesh & Stack, 2001).

The duration of cardiovascular diseases showed a significant relationship with the probability of dying among nine months of hemodialysed patients. In Australia, New Zealand and the United States, cardiovascular disease was reported as the leading cause of death in dialysis patients (Annual Data Report Minneapolis, 2006). In

another study, Mailloux et al. identified the causes of death in maintenance dialysis patients who survived at least 90 days and were monitored during 16 years, and cardiovascular disease was one of the causes of death among those patients (McDonald, 2015). Cardiovascular disease is one of the complications of end-stage renal failure (Marry Anne & Alledredge, 2013), however the statement about correlation between CVD and CKD is still controversial (Herzog et al., 2011).

CONCLUSION

During this study, few practice patterns revealed such as no parathyroid hormone (PTH) level check, no patients got calcimimetic agents such as rocalcitriol/calcitriol and calcium value check was conducted irregularly (only when patients needed it). As we know, there is correlation between PTH, calcium and cardiovascular disease. Hence, mortality due to cardiovascular could be correlated with duration of cardiovascular disease, lack of PTH check, calcium check and no rocalcitriol/calcitriol supplement given to those patients.

ACKNOWLEDGEMENT

We would like to thank Prof. Dr. Markum and Cempaka Putih Islamic Hospital Jakarta for their support in this research. Our gratitude to the Ministry of Education and Research in Indonesia.

CONFLICT OF INTEREST

No conflict of interest

REFERENCES

- Annual Data Report Minneapolis. (2006). *Renal Data System US*.
- Almeida, F. A. De, Ciambelli, G. S., Bertoco, A. L., Jurado, M. M., Siqueira, G. V., Bernardo, E. A., ... Gianini, R. J. (2015). Family Clustering of Secondary Chronic Kidney Disease with Hypertension or Diabetes Mellitus. A Case-Control Study. *Ciência & Saúde Coletiva*, 20(2), 471–478.
- Block, G. A., & Port, F. K. (2000). Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation*, 35(6), 1226–1237. [https://doi.org/10.1016/S0272-6386\(00\)70064-3](https://doi.org/10.1016/S0272-6386(00)70064-3)
- Flanc, R. S., Roberts, M. A., Strippoli, G. F., Chadban, S. J., Kerr, P. G., & Atkins, R. C. (2004). Treatment of

- diffuse proliferative lupus nephritis: a meta-analysis of randomized controlled trials. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*, 43(2), 197–208. <https://doi.org/10.1053/j.ajkd.2003.10.012>
- Ganesh, S. K., Stack, A. G., Levin, N. W., Hulbert-Shearon, T., & Port, F. K. (2001). Association of elevated serum PO₄, Ca x PO₄ product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *Journal of the American Society of Nephrology : JASN*, 12(10), 2131–2138.
- Greten, J., Kreis, I., Wiesel, K., Stier, E., Schmidt, A. M., Stern, D. M., ... Nawroth, P. P. (1996). Receptors for advance glycation end-products (AGE) - expression by endothelial cells in non-diabetic uraemic patients. *Nephrol Dial Transplant*, 11(5), 786–790. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8671895
- Hallan, S. I., & Orth, S. R. (2011). Smoking is a risk factor in the progression to kidney failure. *Kidney International*, 80(5), 516–523. <https://doi.org/10.1038/ki.2011.157>
- Hayen, A., Pellegrini, F., Craig, J. C., & Chb, M. B. (2017). Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death. *JAMA*, 305(11), 1119–1127.
- Herzog, C. A., Asinger, R. W., Berger, A. K., Charytan, D. M., ez, J. D. iacute, Hart, R. G., ... Ritz, E. (2011). Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International*, 80(6), 572–586. <https://doi.org/10.1038/ki.2011.223>
- Indonesian Renal Registry. (2014). *7th Report of Indonesian Renal Registry 2014*.
- Malluche, H. H., Ritz, E., Lange, H. P., Kutschera, J., Hodgson, M., Seiffert, U., ... Lange, H. P. (1976). Bone histology in incipient and advanced renal failure. *Kidney International*, 9(4), 355–362. <https://doi.org/10.1038/ki.1976.42>
- Marry Anne, K.-K., & Alledredge, B. K. (2013). *Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs*.
- McDonald, S. P. (2015). Australia and New Zealand Dialysis and Transplant Registry. *Kidney International Supplements*, 5(1), 39–44. <https://doi.org/10.1038/kisup.2015.8>
- Moe, S. M., Drüeke, T., Lameire, N., & Eknoyan, G. (2007). Chronic Kidney Disease–Mineral-Bone Disorder: A New Paradigm. *Advances in Chronic Kidney Disease*, 14(1), 3–12. <https://doi.org/10.1053/j.ackd.2006.10.005>
- National Kidney Foundation. (2003). K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. *Am J Kidney Dis*, 41(4, Suppl 3), S1–S91. <https://doi.org/S0272638603001197> [pii]
- National Kidney Foundation. (2009). KDIGO Clinical Practice Guideline for the Diagnosis , Evaluation , Prevention , and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). *Kidney International*, 76(August).
- National Kidney Foundation. (2013). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International*, 3(1), Supplement. <https://doi.org/10.1038/kisup.2012.76>
- Nikodimopoulou, M., & Liakos, S. (2011). Secondary hyperparathyroidism and target organs in chronic kidney disease. *Hippokratia*, 15(Suppl 1), 33–38.
- Pitts, T. O., Piraino, B. H., Mitro, R., Chen, T. C., Segre, G. V., Greenberg, A., & Puschett, J. B. (1988). Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. *The Journal of clinical endocrinology and metabolism*, 67(5), 876–881. <https://doi.org/10.1210/jcem-67-5-876>.
- Venícios, M., Lopes, D. O., Luisa, A., & Carvalho, B. De. (2017). Excess fluid volume : sociodemographic and clinical analysis in haemodialysis patients. *Rev Bras Enferm (REBEn)*, 70 (1), 11–17.