# Prevalence of proteinuria among the Orang Asli aborigines and ethnic minorities of Malaysia

and

# Survival of elderly and non-elderly end stage renal failure patients with and without dialysis

By

Chin Chin Ch'ng

Thesis

Submitted in partial fulfilment of the requirements for the Degree of Master of Public Health in the Brown University School of Public Health

PROVIDENCE, RHODE ISLAND

MAY 2019

This thesis by ***Chin Chin Ch'ng*** is accepted in its present form by the Brown University School of Public Health as satisfying the thesis requirements for the degree of Master of Public Health.

Date_____

_____

Loke Meng Ong, FRCP, Advisor

Date_____

_____

Stephen McGarvey, PhD, Reader

Date_____

_____

Annie Gjelsvik, PhD
Associate Director, Master of Public Health Program

Approved by the Graduate Council

Date_____

_____

Andrew G. Campbell, Dean of the Graduate School

## Preface and Acknowledgements

This thesis would not have been possible without all those who had assisted in these projects. First of all I would like to thank my thesis advisor, Dr Loke Meng Ong, FRCP, for his guidance on these studies and his continued support throughout my career. His expertise and enthusiasm for renal research is to be lauded for. In addition, I would like to thank my thesis reader, Dr Stephen McGarvey, PhD, for his insightful feedback and invaluable advice. I would also like to extend my appreciation to Dr Omar Galarraga, PhD for his advice throughout my graduate academic career and Joann Barao for her unwavering support and assistance.

Table of contents

List of tables and figures

**PART I: RESEARCH PAPER - PREVALENCE OF PROTEINURIA AMONG THE ORANG ASLI ABORIGINES AND ETHNIC MINORITIES OF MALAYSIA**



**PART II: RESEARCH PAPER - SURVIVAL OF ELDERLY AND NON-ELDERLY END STAGE RENAL FAILURE PATIENTS WITH AND WITHOUT DIALYSIS**

# PREVALENCE OF PROTEINURIA AMONG THE ORANG ASLI ABORIGINES AND ETHNIC MINORITIES OF MALAYSIA

## INTRODUCTION

Malaysia is divided by the South China Sea into Peninsular Malaysia (West Malaysia) and East Malaysia (comprising Sabah and Sarawak on the Malaysian Borneo). The Malaysian population is made up of slightly more than 50% of Malays, close to 24% of Chinese, 7% of Indians, 11% of natives of Sabah and Sarawak and 0.7% of the Orang Asli aborigines (1). Both regions are ethnically diverse however, most of the population are concentrated in the more developed Peninsular Malaysia, and are predominantly Malay, Chinese and Indian. The Orang Asli aborigines mostly reside in rural or undeveloped areas of Peninsular Malaysia, largely in the states of Pahang and Perak (2). In East Malaysia, the natives of Sabah and Sarawak make up a large proportion of its population. There are over 30 ethnic groups in Sabah and Sarawak such as the Kadazan, Dusun, Murut, Bajau, Iban, Bidayuh, Melanau, and Orang Ulu (3).

The term Orang Asli is literally translated as 'natural people' and is a Malay term taken to mean the 'original' or 'first' peoples of Peninsular Malaysia. The term is used to collectively describe the different aboriginal sub-ethnicities in Peninsular Malaysia. The aborigines can be separated into three genetically distinct lineages of people, known as the Semang (Negrito), Senoi and Proto-Malay (2). Possibly due to their relative isolation, the aborigines were known to still maintain aspects of their respective languages, spiritual values, cultures and social organizations that are distinct from other populations in Malaysia (1,2). Most of the aborigines' villages are located in the outskirts of rural villages and remote areas while only 2% are located at the vicinity of townships. Throughout this paper we will use the term aborigines when referring to the Orang Asli.

Since 1970, there has been a slow and gradual migration of aborigines from rural to urban areas of Peninsular Malaysia and in year 2000, the census showed 11.3% of aborigines had settled in urban areas (4). However, majority of them still reside in isolated areas and beneath the poverty line, rendering them inaccessible to services such as healthcare. The ethnic minorities of Sabah and

Sarawak have a better political position than the aborigines however, socio-economically many of them still lag behind other major races, especially to those in Peninsular Malaysia (2).

The government has worked on developing a good, inclusive network of health care, education and other services throughout the country to include rural areas (5,6). Despite these efforts, major coordination, logistical and synchronization issues with these communities have often led to continual lack of access to such services (2). Many of the aborigines and ethnic minorities still practice traditional medicine and there exists a gap in health care beliefs. The Semai, for example, uses traditional treatments such as herbs within their traditional health system that exists in small clusters of communities that ensure the thriving of each community member (7). Some smaller subtribes such as the Lanoh and Bateq still prefer the nomadic lifestyle despite government provided infrastructures (8).

The aborigines and ethnic minorities in Malaysia have not been very well represented in health research. Most research and data collection were done in Peninsular Malaysia and few were extended to include Sabah and Sarawak or rural and undeveloped regions of Peninsular Malaysia (9). However, because these groups may be different from the larger general population genetically and socio-culturally, it is important that health research include them. In the few studies that were focused on the aborigines and ethnic minorities, differences in disease risks and health status have been found.

In a retrospective study conducted in the three major aborigine tribes, the authors found that the Proto-Malays, the group that had the most urbanized lifestyle of the three, had the highest prevalence of metabolic syndrome, suggesting a possible epidemiologic transition (10). Phipps et al. found differences in rates of obesity, abdominal-obesity, hypertension, pre-diabetes and diabetes among seven subtribes of aborigines that could possibly also be attributed to lifestyle and proximity to large cities (11). Another study hypothesized that aborigines that live inland may be

healthier than those who live in peripheries of towns. However, when the authors compared aborigines in the inland and peripheries of towns to urban Malays, they found that the aborigines had elevated risks of cardiovascular disease, with the highest among those in the inland, followed by those in the periphery and finally the Malays (8). They also found high insulin levels among the aborigines compared to Malays. These suggests that not just location but other factors including lifestyle, culture and beliefs, and inherent genetic predisposition may also be causing the observed differences in risk.

One of the diseases that has been on the rise in Malaysia is chronic kidney disease (CKD). The prevalence of CKD in Peninsular Malaysia was estimated to be 9.07% with 0.36% in Stage 5 progressing to end stage renal disease where renal replacement therapy is inevitable (12). Although more private and public dialysis centers have opened in Malaysia, they may not be able to keep up with the present and future needs. Free, public dialysis centers are extremely limited with long waiting lists and private ones are expensive. Furthermore, most are located in urban areas, creating issues for those who live in the outskirts and remote areas of the country. Thus, prevention is the best solution to this impending epidemic.

In light of this, the National Kidney Foundation (NKF) of Malaysia launched a mobile health screening program in January 2008 to promote early detection and prevention of kidney disease. One of the screening services offered was proteinuria testing. Proteinuria, a condition where excessive protein is excreted in the urine, may be an early sign of kidney damage and a strong marker for progression of CKD (13). Kidney damages, specifically dysfunction of glomerular filtration and tubular resorption, may result in increased urinary excretion of albumin, a type of protein, leading to proteinuria.

In the NKF Lifecheck Health Screening program conducted in all states in Malaysia, proteinuria was detected in 1.4% of its participants (14). However, most of these screenings were

held in urban areas and participation from aborigines and other ethnic minorities were limited. Therefore data from these screenings may not be representative of that in these communities. Thus, in September 2014, the NKF expanded these screening programs to rural areas of the country.

This study aimed to determine the prevalence and risk factors of proteinuria in the aborigines and other ethnic minorities compared to the rest of the population. We approached this through two perspectives. First, we hypothesized that lifestyle may play a bigger role in determining risk of proteinuria and compared the risk based on the participant's residence, whether they lived in rural and remote villages or in non-rural areas. Second, we hypothesized that inherent characteristics such as genetics is a more important determinant. Here, we compared the risk based on ancestry and ethnicity of the participants, regardless of where they were located.

## METHODS

### *Research design and study population*

This was a cross-sectional study using secondary data from a health screening survey conducted by the National Kidney Foundation (NKF). The NKF conducted a nationwide NKF Lifecheck Health Screening program between September 2014 and January 2015 in both rural and non-rural locations in Malaysia. The public, including the aborigines, ethnic minority groups and the general population (hereby used to refer to all other population of Malaysia except the aborigines and ethnic minorities of Sabah and Sarawak) were invited to participate in the health screening. Each participant completed a survey form on basic demographic, smoking, exercise and medical and family history of illness before their blood pressure (BP), body mass index (BMI) and waist circumference measurements were taken. Urine testing for glucose, protein, blood and

ketone were done whenever possible. In one village, urine testing was not carried out due to absence of water supply. The participants can also have their blood glucose and cholesterol tested. This study used de-identified secondary data and approval from an institutional review board was not required.

*Inclusion and exclusion criteria*

Only participants aged 18 years and above with complete data were included in the analysis. Since the health screenings were open to everyone, we excluded non-Malaysians who had participated in the survey from the analysis. Participants with missing values or who did not test for urine protein were also excluded.

*Exposure groups*

We were interested to study the effects of location of residence and inherent ancestry and ethnicity differences on risk of proteinuria. In the first analysis, the primary exposure was area of residence. Participants were grouped based on whether they lived in rural villages or otherwise, regardless of ancestry or ethnicity. In the second analysis, the primary exposure was ancestry and ethnicity. In this analysis, the aborigines and ethnic minorities were categorized together as a group and compared with the "general population" comprising Malays, Chinese and Indians.

*Outcome*

The outcome of interest was proteinuria. Random spot urine test was carried out during the screenings using the 'URiSCAN Optima II' urine chemistry analyzer. Proteinuria was defined as the presence of protein in the urine of at least + (30 mg/dL).

**Statistical analysis**

Continuous variables were summarized as means and standard deviations while categorical variables were expressed as frequencies and percentages. Unadjusted and adjusted logistic regression was carried out to determine the odds ratio of proteinuria. In the first analysis, risk of proteinuria was compared based on area of residence and in the second analysis, the risk was compared based on ancestry/ethnicity. We also explored factors that may be associated with risk of proteinuria using multiple logistic regression in a model with all covariates. Analysis was performed using STATA 11. A p-value of <0.05 was considered statistically significant.

RESULTS

Within the 5-month screening period, 10921 participants were screened. After excluding non-Malaysians, participants aged below 18 years old and those that had missing baseline data or missing urine protein results, 8649 patients were included in the analysis (Figure 1). The characteristics of the participants by area of residence are shown in Table 1. Most aborigines and ethnic minorities lived in rural areas.

Table 2 shows the distribution of proteinuria in the population. The prevalence of proteinuria in the rural villages was 5.0% while in the non-rural areas it was 1.6%. Based on ancestry and ethnicity, the prevalence of proteinuria was 1.7% in the general population which consists of Malay, Chinese and Indians and 3.3% and 4.8% in the aborigines and ethnic minority groups, respectively. Among the general population, the Malays had the highest prevalence (2.0%) followed by the Indians at 1.4% and the Chinese at 1% (data not shown).

The unadjusted and adjusted odds ratio for proteinuria are shown in Table 3. There was a higher risk of proteinuria among those who live in rural villages compared to those who live in

non-rural areas (unadjusted OR 3.27, 95% CI 2.15, 4.97, p-value <0.001; adjusted OR 2.53, 95% CI 1.39, 4.58, p-value = 0.002). The study failed to show any significant differences in risk of proteinuria among the aborigines and ethnic minorities compared with the Malay, Chinese and Indians, after adjusting for covariates (adjusted OR 1.09, 95% CI 0.53, 2.22, p-value = 0.818). When we compared just the subgroup of aborigines with the rest of the population we saw a lower risk of proteinuria in the aborigines however, the difference was also not significant (adjusted OR 0.70, 95% CI 0.21, 2.26, p-value = 0.546). We found a higher risk in the aborigines compared with ethnic minorities alone however, it was not significant (adjusted OR 1.49, 95% CI 0.31, 7.26, p-value = 0.623).

In an exploratory analysis to investigate factors associated with risk of proteinuria, we found females to have a lower risk of proteinuria compared to males (adjusted OR 0.67, 95% CI 0.45, 0.98, p-value = 0.041) (Table not shown). The Chinese also had a statistically significantly lower risk of proteinuria compared to the Malay (adjusted OR 0.58, 95% CI 0.36, 0.94, p-value = 0.028). On the other hand, people who lived in rural areas had a higher risk of proteinuria (adjusted OR 2.53, 95% CI 1.40, 4.58, p-value = 0.002). As expected, participants with diabetes mellitus (adjusted OR 3.99, 95% CI 2.69, 5.09, p-value <0.001), hypertension (adjusted OR 2.27, 95% CI 1.54, 3.35, p-value <0.001) or CKD (adjusted OR 7.41, 95% CI 3.38, 16.23, p-value <0.001) had increased risk of proteinuria.

## DISCUSSION

This is the first population-based study to determine prevalence of proteinuria among the aborigines and ethnic minorities in Malaysia and comparing their risk of proteinuria to the general population. Prevalence of proteinuria was higher in the rural villages compared to the non-rural

areas. Prevalence of proteinuria was also elevated among the aborigines and ethnic minorities compared with the general population comprising Malay, Chinese and Indians.

We found that the risk for proteinuria was higher among those who lived in rural areas compared to those in the non-rural areas. However, there was no significantly elevated risk of proteinuria among the aborigines and ethnic minorities compared with the rest of the population, indicating that where a person lived may be a more important predictor of proteinuria and kidney disease than race and ethnicity.

*Previous studies*

Relatively few studies have been carried out to study health status of indigenous populations of Malaysia. Even fewer have compared their risk of diseases to the general population. Studies that have been done have shown high prevalence of cardio-metabolic health risks in this group of people. As far as we are aware, no study has been published on prevalence of proteinuria or risks of kidney disease in the aborigines and ethnic minorities of Sabah and Sarawak. Most previous studies that involved the indigenous were only carried out within the group, making comparison with the general population difficult.

In a study comparing different subtribes of aborigines, Phipps et al. found varying prevalence for obesity, cholesterol, hypertension and diabetes between the subtribes (11). The authors concluded that the differences may be likely due to genetic predisposition, lifestyle changes and socio-economic effects and that the cardio-metabolic risk factors may worsen with further urbanization. Similarly, in another study, differential risks of metabolic syndrome were found among different subtribes which the author have also attributed to rapid urbanization (10). However, because these studies looked at a different outcome and did not follow the population over time or compared them to the general population, it is difficult to infer if there was any

difference between the aborigines and the other population of Malaysia and if the differences seen were due to genetic predispositions or where they lived.

In our study, we compared the aborigines and ethnic minorities to the general population and found that location where people lived was a more important determinant for risk of proteinuria than inherent differences between ancestry and ethnicity. We found that risks were higher among those who lived in rural areas, which contradicted the hypothesis proposed by previous studies on negative effects of urbanization on health and perceptions that people who lived inland were healthier.

In a local study on risks of cardiovascular diseases comparing different subtribes of aborigines with urban Malays, a similar pattern in risks by location was observed (8). The authors found higher cardiovascular risk scores among aborigines living inland compared with those living at the periphery of towns. The aborigines also had higher incidences of low HDL-c levels compared with urban Malays, indicating that there may be other stronger explanation for the observed differences than urbanization alone.

Our results were in agreement with the findings of a study from Cameroon on risk on CKD comparing rural and urban populations. Kaze et al. observed a higher prevalence of albuminuria, defined as an albumin to creatinine ratio of ≥30 mg/g, in rural compared to urban population (15). The observation in China however was different. A rural Zhuang ethnic minority population in China exhibited lower prevalence of CKD when compared with other parts of the country and with other developed and developing countries (16). In Taiwan, children born to both parents of aboriginal descent had lower odds ratio of proteinuria compared to those whose parents were both non-aboriginals (17). The authors credited the observation to possible ethnic differences in urine protein excretion.

The varying risks found in rural and indigenous communities of different countries meant that genetic predisposition could be at play. However, in our study, we could not attribute the difference in risk in rural areas compared to non-rural areas to genetic predisposition alone because we did not find any significant differences in risk when we compared the aborigines and ethnic minorities with other races. It is possible that not just genetics but a myriad of other interacting factors such as lifestyle, rural medical and diet beliefs and practices and access to healthcare could play a role in the observed difference in risk.

The aborigines in Malaysia has developed their own community health system based on traditional knowledge passed on from one generation to another (7). To them, this system involving herbal treatments has been providing the essential care that they needed. Additionally, economic reasons, fear, misunderstandings or lack of trust by the rural minorities for the modern healthcare system may make early detection and diagnosis of diseases impossible (18). Compared to the general population, a higher proportion of rural minorities remain unaware of their disease status (15,16).

CKD is a silent disease and a large proportion of people with CKD remain unaware until it is too late. Our finding that rural areas have a higher prevalence of proteinuria suggests possible early indication of chronic kidney disease. Because CKD is a costly disease, cost-effective measures for frequent screening for risk factors and early signs are essential to slow progression to advanced renal disease and minimize associated complications and medical costs. Thus, it is important to ensure continual, quality access to health screening for populations in rural and remote areas of Malaysia which lack mainstream healthcare services. In Canada, mass screening for CKD in remote, high-risk indigenous communities have been proved to be more cost-effective than usual care (19). Other cost-effective methods have also been studied, such as using CKD risk scores to identify persons for CKD screening, generating a more targeted approach to save costs (20).

*Strengths and limitations*

To the best of our knowledge, this study is the first and only population-based study in Malaysia reporting prevalence of proteinuria in the aborigines and ethnic minorities of Sabah and Sarawak and their risks compared with the general population of the country.

This study has several limitations. Firstly, the data collected from the NKF survey were cross-sectional. The measurements on urine protein were based on a single measurement, making it impossible to determine if the proteinuria detected were persistent or transient, given that levels of protein in the urine can fluctuate based on external influences such as recent diet, medication and vigorous exercise or on acute conditions such as urinary tract infection, fever and stress (21,22). Thus the prevalence obtained may be an overestimation.

Secondly, as information on addresses were not collected, the category for rural and non-rural residence was based on the location where the participant had taken done the screening. Therefore, we could not determine if a participant had moved from a rural village and the duration he or she had been living in urban cities. Thus, the effects of relocation or changes in lifestyle could not be accounted for.

Thirdly, participation in the screening and survey was voluntary thus the data may be prone to selection bias and may not be representative of the true population.

*Future research*

Further studies on aborigines and other rural ethnic minorities with longitudinal screening and follow up are required to provide a more reliable picture of the prevalence of proteinuria and chronic kidney disease to assist better decision making and healthcare budget allocation.

## CONCLUSION

Prevalence of proteinuria were higher in rural areas of Malaysia and among aborigines and ethnic minorities of Sabah and Sarawak. Living in a rural area is a stronger predictor of proteinuria than inherent ancestry and ethnicity differences. Therefore, focusing resources on screening for chronic kidney disease in rural areas may be more cost-effective in the long run.

REFERENCES

1. Subramaniam Y. Ethnicity, Indigeneity and Indigenous Rights: The "Orang Asli" Experience. QUT Law Rev [Internet]. 2015 Nov 2 [cited 2019 Mar 10];15(1). Available from: https://lr.law.qut.edu.au/article/view/562

2. Masron T, Masami F, Ismail N. Orang Asli in Peninsular Malaysia: population, spatial distribution and socio-economic condition. J Ritsumeikan Soc Sci Humanit. 2013;6:75–115.

3. David MK, Dealwis C. Why Shift? Focus on Sabah and Sarawak. Suvremena Lingvistika. 2008;34(66).

4. Khor GK, Zalilah MS. The ecology of health and nutrition of Orang Asli (Indigenous people) women and children in Peninsular Malaysia. Tribes Tribals. 2008;2:66–77.

5. Krishnaswamy S, Subramaniam K, Low WY, Aziz JA, Indran T, Ramachandran P, et al. Factors contributing to utilization of health care services in Malaysia: a population-based study. Asia Pac J Public Health. 2009 Oct;21(4):442–50.

6. Noor M, Asri M. Advancing the Orang Asli through Malaysia's clusters of excellence policy. J Int Comp Educ. 2012;1(2):90–103.

7. Wong YS, Allotey P, Reidpath DD. Sustainable development goals, universal health coverage and equity in health systems: the Orang Asli commons approach. Glob Health Epidemiol Genomics. 2016;1:e12.

8. Tuan Abdul Aziz TA, Teh LK, Md Idris MH, Bannur Z, Ashari LS, Ismail AI, et al. Increased risks of cardiovascular diseases and insulin resistance among the Orang Asli in Peninsular Malaysia. BMC Public Health. 2016 Mar 24;16:284.

9. Leete R, Kwok KK. Demographic Changes in East Malaysia and their Relationship with those in the Peninsula 1960–80. Popul Stud. 1986;40(1):83–100.

10. Aghakhanian F, Wong C, Tan JSY, Yeo LF, Ramadas A, Edo J, et al. Metabolic syndrome and cardiometabolic risk factors among indigenous Malaysians. Public Health. 2018 Nov 30;

11. Phipps ME, Chan KKL, Naidu R, Mohamad NW, Hoh B-P, Quek K-F, et al. Cardio-metabolic health risks in indigenous populations of Southeast Asia and the influence of urbanization. BMC Public Health. 2015 Jan 31;15:47.

12. Hooi LS, Ong LM, Ahmad G, Bavanandan S, Ahmad NA, Naidu BM, et al. A population-based study measuring the prevalence of chronic kidney disease among adults in West Malaysia. Kidney Int. 2013 Nov;84(5):1034–40.

13. Gorriz JL, Martinez-Castelao A. Proteinuria: detection and role in native renal disease progression. Transplant Rev Orlando Fla. 2012 Jan;26(1):3–13.

14. Ong LM, Punithavathi N, Thurairatnam D, Zainal H, Beh ML, Morad Z, et al. Prevalence and risk factors for proteinuria: the National Kidney Foundation of Malaysia Lifecheck Health Screening programme. Nephrol Carlton Vic. 2013 Aug;18(8):569–75.

15. Kaze FF, Meto DT, Halle M-P, Ngogang J, Kengne A-P. Prevalence and determinants of chronic kidney disease in rural and urban Cameroonians: a cross-sectional study. BMC Nephrol. 2015 Jul 30;16:117.

16. Pan L, Ma R, Wu Y, Feng L, Song Y-S, Ye X-D, et al. Prevalence and risk factors associated with chronic kidney disease in a Zhuang ethnic minority area in China. Nephrol Carlton Vic. 2015 Nov;20(11):807–13.

17. Chen M-C, Wang J-H, Chu C-H, Cheng C-F. Differential prevalence of hematuria and proteinuria with socio-demographic factors among school children in Hualien, Taiwan. Pediatr Neonatol. 2018;59(4):360–7.

18. Shahid S, Teng T-HK, Bessarab D, Aoun S, Baxi S, Thompson SC. Factors contributing to delayed diagnosis of cancer among Aboriginal people in Australia: a qualitative study. BMJ Open. 2016 03;6(6):e010909.

19. Ferguson TW, Tangri N, Tan Z, James MT, Lavallee BDA, Chartrand CD, et al. Screening for chronic kidney disease in Canadian indigenous peoples is cost-effective. Kidney Int. 2017;92(1):192–200.

20. Yarnoff BO, Hoerger TJ, Simpson SK, Leib A, Burrows NR, Shrestha SS, et al. The cost-effectiveness of using chronic kidney disease risk scores to screen for early-stage chronic kidney disease. BMC Nephrol. 2017 Mar 13;18(1):85.

21. Amin N, Zaritsky JJ. Proteinuria. In: Bajaj L, Hambidge SJ, Kerby G, Nyquist A-C, editors. Berman's Pediatric Decision Making (Fifth Edition) [Internet]. Saint Louis: Mosby; 2011. p. 768–71. Available from: http://www.sciencedirect.com/science/article/pii/B9780323054058001777

22. Sreedharan R. 19 - Proteinuria. In: Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, editors. Nelson Pediatric Symptom-Based Diagnosis [Internet]. Elsevier; 2018. p. 312–320.e1. Available from: http://www.sciencedirect.com/science/article/pii/B9780323399562000194

TABLES AND FIGURES

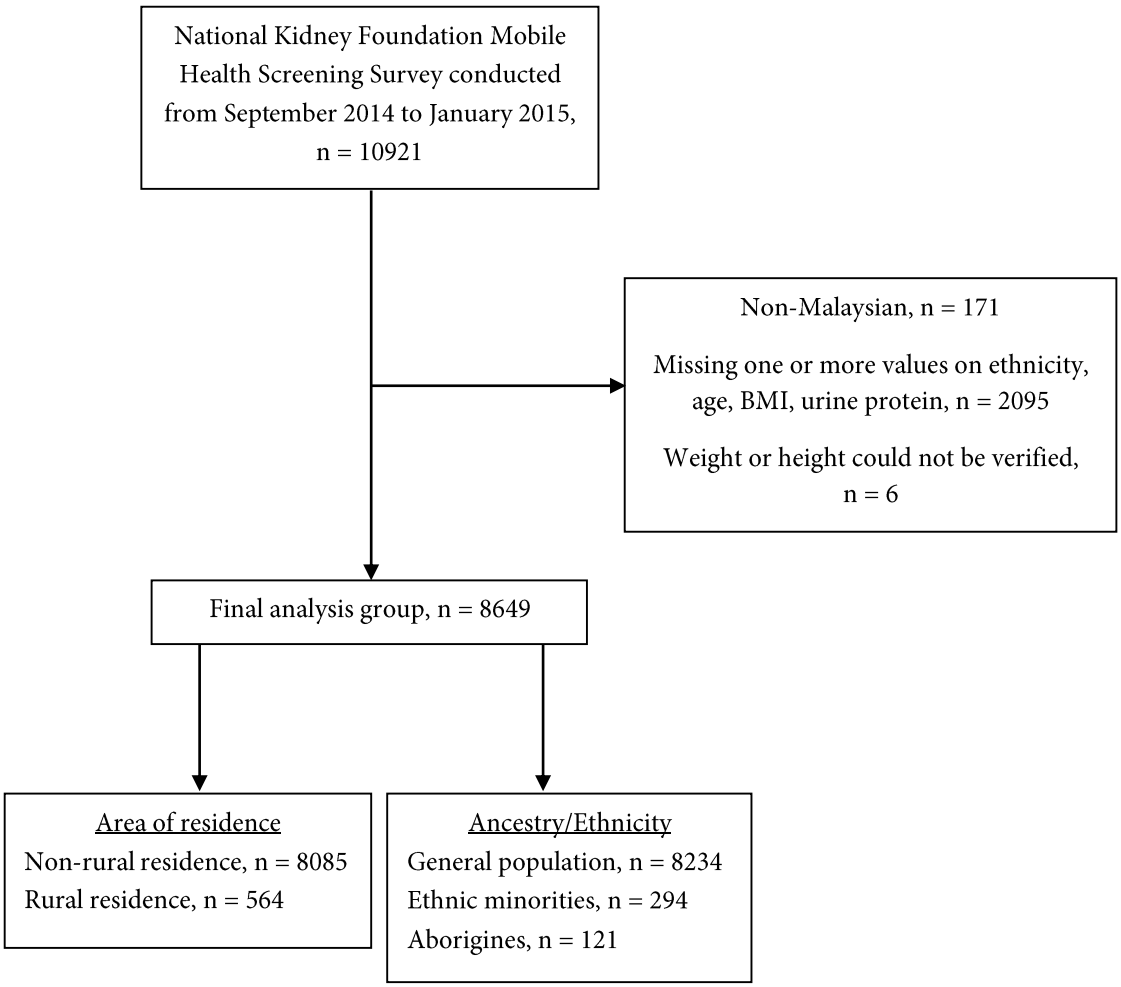



Figure 1. Flowchart of participant inclusion and exclusion

Table 1. Characteristics by area of residence and by ancestry/ethnicity, n = 8649

| **Characteristics** | **Area of residence** | | **Ancestry/Ethnicity** | | |
|---|---|---|---|---|---|
| | **Non-rural residence, n = 8085** | **Rural residence, n = 564** | **General population[a], n = 8234** | **Aborigines, n = 121** | **Ethnic minorities, n = 294** |
| Age (years), mean (SD) | 42.7 (14.4) | 45.7 (14.6) | 42.8 (14.4) | 39.2 (13.7) | 47.3 (15.0) |
| Gender, n (%) | | | | | |
| Male | 4152 (51.4) | 270 (47.9) | 4236 (51.5) | 42 (34.7) | 144 (49.0) |
| Female | 3933 (48.7) | 294 (52.1) | 3998 (48.6) | 79 (65.3) | 150 (51.0) |
| Ancestry/ Ethnicity, n (%) | | | | | |
| Malay | 4871 (60.3) | 198 (35.1) | 5069 (61.6) | - | - |
| Chinese | 2121 (26.2) | 46 (8.2) | 2167 (26.3) | - | - |
| Indian | 991 (12.3) | 7 (1.2) | 998 (12.1) | - | - |
| Aborigines | 4 (0.05) | 117 (20.7) | - | 121 (100) | - |
| Ethnic minorities | 98 (1.2) | 196 (34.8) | - | - | 294 (100) |
| BMI ($kg/m^2$), mean (SD) | 25.9 (4.9) | 27.2 (5.1) | | | |
| Underweight (<18.5), n (%) | 337 (4.2) | 17 (3.0) | 342 (4.2) | 2 (1.7) | 10 (3.4) |
| Normal weight (18.5 to <25), n (%) | 3384 (41.9) | 181 (32.1) | 3425 (41.6) | 34 (28.1) | 106 (36.1) |

| | | | | | |
|---|---|---|---|---|---|
| Overweight (25 to <30), n (%) | 2906 (35.9) | 220 (39.0) | 2963 (36.0) | 40 (33.1) | 123 (41.8) |
| Obese (≥30), n (%) | 1458 (18.0) | 146 (25.9) | 1504 (18.3) | 45 (37.2) | 55 (18.7) |
| Education, n (%) | | | | | |
| Nil | 209 (2.6) | 69 (12.2) | 213 (2.6) | 24 (19.8) | 41 (14.0) |
| Primary | 730 (9.0) | 194 (34.4) | 779 (9.5) | 72 (59.5) | 73 (24.8) |
| Secondary | 3332 (41.2) | 239 (42.4) | 3419 (41.5) | 24 (19.8) | 128 (43.5) |
| College/University/Vocational studies | 3814 (47.2) | 62 (11.0) | 3823 (46.4) | 1 (0.8) | 52 (17.7) |
| Smoking, n (%) | 1716 (21.2) | 141 (25.0) | 1761 (21.4) | 23 (19.0) | 73 (24.8) |
| Exercise, n (%) | | | | | |
| No exercise | 3733 (46.2) | 336 (59.6) | 3828 (46.5) | 102 (84.3) | 139 (47.3) |
| <3 times/week | 2559 (31.7) | 123 (21.8) | 2593 (31.5) | 11 (9.1) | 78 (26.5) |
| ≥3 times/week | 1793 (22.2) | 105 (18.6) | 1813 (22.0) | 8 (6.6) | 77 (26.2) |
| Diabetes mellitus, n (%) | 694 (8.6) | 48 (8.5) | 707 (8.6) | 5 (4.1) | 30 (10.2) |
| Hypertension, n (%) | 1287 (15.9) | 126 (22.3) | 1321 (16.0) | 22 (18.2) | 70 (23.8) |
| Chronic kidney disease, n (%) | 45 (0.6) | 5 (0.9) | 47 (0.6) | 0 | 3 (1.0) |

[a] General population consist of Malay, Chinese and Indian races

Table 2. Distribution of proteinuria by area of residence and ancestry/ethnicity

| **Urine protein** | **Area of residence** | | **Ancestry/Ethnicity** | | |
|---|---|---|---|---|---|
| | **Non-rural residence, n = 8085** | **Rural residence, n = 564** | **General population[a], n = 8234** | **Aborigines, n = 121** | **Ethnic minorities, n = 294** |
| Negative, n (%) | 7790 (96.4) | 515 (91.3) | 7924 (96.2) | 112 (92.6) | 269 (91.5) |
| Trace (10 mg/dL), n (%) | 168 (2.1) | 21 (3.7) | 173 (2.1) | 5 (4.1) | 11 (3.7) |
| + (30 mg/dL), n (%) | 68 (0.8) | 16 (2.8) | 73 (0.9) | 2 (1.7) | 9 (3.1) |
| ++ (100 mg/dL), n (%) | 51 (0.6) | 9 (1.6) | 55 (0.7) | 2 (1.7) | 3 (1.0) |
| +++ (300 mg/dL), n (%) | 7 (0.1) | 2 (0.4) | 7 (0.1) | 0 | 2 (0.7) |
| ++++ (1000 mg/dL), n (%) | 1 (0.01) | 1 (0.2) | 2 (0.02) | 0 | 0 |

[a] General population consist of Malay, Chinese and Indian races

Table 3. Unadjusted and adjusted odds ratios[a] for proteinuria based on area of residence and ancestry/ethnicity[b]

| | Proportion | Unadjusted OR (95% CI) | p-value | Adjusted OR (95% CI) | p-value |
|---|---|---|---|---|---|
| Lived in rural areas | 564/8649 | 3.27 (2.15, 4.97) | <0.001 | 2.53 (1.39, 4.58)[c] | 0.002 |
| Aborigines and ethnic minorities combined | 415/8649 | 2.67 (1.62, 4.43) | <0.001 | 1.09 (0.53, 2.22)[d] | 0.818 |
| Aborigines[e] | 121/8355 | 2.02 (0.74, 5.55) | 0.173 | 0.70 (0.21, 2.26)[d] | 0.546 |
| Ethnic minorities[f] | 294/8528 | 2.96 (1.68, 5.19) | <0.001 | 1.19 (0.56, 2.51)[d] | 0.651 |

*OR* odds ratio, *CI* confidence interval

[a] Logistic regression

[b] Aborigines and ethnic minorities were combined, compared to major population (Malay, Chinese, Indian)

[c] Adjusted for ancestry/ethnicity, age, gender, body mass index, education, smoking status, exercise, diabetes mellitus, hypertension, chronic kidney disease

[d] Adjusted for area of residence, body mass index, education, smoking status, exercise, diabetes mellitus, hypertension, chronic kidney disease

[e] Analysis comparing aborigines and the general population (Malay, Chinese, Indian); proportion excludes ethnic minorities

[f] Analysis comparing ethnic minorities and the general population (Malay, Chinese, Indian); proportion excludes aborigines

# SURVIVAL OF ELDERLY AND NON-ELDERLY END STAGE RENAL FAILURE PATIENTS WITH AND WITHOUT DIALYSIS

## INTRODUCTION

Prevalence of chronic kidney disease (CKD) is on the increase worldwide. According to the Global Burden of Disease study, CKD contributed a total of 8.77 million (95% uncertainty interval 6.60 to 11.10 million) years lived with disability globally in 2016, an increase of 3.8% in age-standardized rates from 2006 (1). CKD is a disease that progresses with age (2), with end stage renal failure (ESRD) manifesting with duration of risk exposure. The proportion of population over 60 years old is postulated to double from 12% in 2015 to 22% in 2050 (3). With these rising numbers of elderly people around the world, CKD and ESRD will inevitably become an increasing health burden in the near future.

In Malaysia, CKD is the 9$^{th}$ most common cause of death, with an age-standardized premature mortality rate of 351.7 per 100,000 population in 2016 (4). Although data on incidence of CKD and ESRD in Malaysia is unknown, prevalence of CKD in Peninsular Malaysia was estimated to be at 9.07%, out of which 0.36% were CKD Stage 5 (5). Going hand in hand with that, more dialysis centers have opened in Malaysia, and dialysis acceptance rates have almost doubled from 138 per million population (pmp) in 2006 to 261 pmp in 2015 (6).

A study estimated the number of incident dialysis patients in Malaysia to increase from 6,985 in 2013 to 10,208 in 2020 and 19,418 in 2040 (7). However, based on present trends, many patients still do not go on dialysis for a multitude of reasons such as financial and logistic difficulties, social stigma or beliefs, long waiting lists or the belief that dialysis offered no benefit (8). The number of estimated dialysis patients could actually be higher if more ESRD patients start to adopt dialysis in the future.

In the elderly, decisions to commence dialysis can be complicated because of co-morbidities, prognosis, quality of life, and treatment burden (9). In some studies, it was found that dialysis offered no survival advantage over conservative management in old patients (10) or in old patients

with high comorbidities (9,11). However, these studies were either too small, susceptible to immortal time bias or were done among patients who had had systematic education on treatment strategies prior to progressing to ESRD.

Currently, the national renal registry reports outcomes of patients on dialysis. However, the outcomes of ESRD patients before commencing dialysis is not well described. Most studies have been carried out only among dialyzed patients. In the few studies that looked at patients before initiation of dialysis, many limited the population to pre-ESRD kidney patients. In two small studies on patients with CKD Stage 5, the mortality rates ranged between 8.3% and 12.1% and the renal replacement rates were between 55.2% and 64.5% after a variable length of follow up (12,13).

However, these studies did not specifically address the period after ESRD diagnosis but before receiving renal replacement therapy. Thus, there is a need to study the outcome among patients after diagnosis of ESRD but before initiation of dialysis and to compare the outcomes before and after dialysis among the elderly and non-elderly. It is also important to understand characteristics of patients less likely to initiate or be initiated on dialysis so appropriate targeted measures can be taken to improve survival in ESRD.

This study was based on an observational cohort and no systematic patient education interventions were applied, thus better reflecting real-world scenarios. Additionally, we compared hazard of death of dialysis only among patients who have reached ESRD and deemed to require dialysis by their physicians, not like some studies which looked at CKD patients who may not yet require dialysis.

Most importantly, we set out to categorize time before dialysis initiation as unexposed time, and time after dialysis initiation as exposed time, to prevent immortal time bias. Immortal time bias is present when patients were categorized as dialyzed or non-dialyzed based on whether the patient ever had dialysis with no regard to the time dialysis was initiated. If not controlled for, this

would confer a dialyzed patient an artificial survival advantage as they would have to survive up to and after the time of dialysis initiation. By treating dialysis as a time-dependent variable, we have prevented immortal time bias.

The primary aim of this study was to determine survival of elderly and non-elderly ESRD patients after commencing dialysis compared to no dialysis. The secondary aim was to examine factors associated with death in elderly and non-elderly dialyzed patients.

## METHODS

### *Research design and study population*

This was an observational cohort study of ESRD patients under follow-up in 44 public dialysis centers in Peninsular Malaysia between 1 January 2007 and 31 December 2008. The cohort contained data on both prevalent ESRD patients and incident patients who were diagnosed with ESRD in the centers during the two year period. The cohort was linked to the National Renal Registry and the National Registration Department to determine dialysis and mortality statuses respectively. The patients were followed until 31 December 2014. This study used de-identified secondary data and approval from an institutional review board was not required.

### *Inclusion and exclusion criteria*

Prevalent ESRD patients who were transferred into the centers or patients who were already on dialysis were excluded from the analysis. Only incident ESRD patients were included and they were diagnosed based on the discretion of the treating nephrologist or if the estimated glomerular filtration rate (eGFR) was below 10 ml/min/1.73m$^2$ with evidence of uremia, fluid overload, malnutrition or contracted kidney(s). Patients under 18 years old or non-Malaysian citizens, with one or more missing values, or with unverifiable dialysis initiation or death dates were also

excluded. The final study sample consisted of 3990 incident ESRD patients who were diagnosed with the disease between 1 January 2007 and 31 December 2008 and eligible for dialysis during the follow-up period.

*Exposure and covariates*

Dialysis was the primary exposure and was treated as a time-dependent variable. Elderly was defined to be aged 65 years and above. Dialysis modality, either hemodialysis or peritoneal dialysis, was taken to be the modality the patient was initiated with. Time-independent covariates were determined at time of ESRD diagnosis. These were age, gender, race, education level, income group, smoking status, diabetes mellitus, hypertension, ischemic heart disease and congestive cardiac failure status and eGFR measurement category (either above or below 10 ml/min/1.73m$^2$).

*Outcome and follow-up*

The primary outcome of interest was all-cause mortality. Patients contributed person-time from the date of ESRD diagnosis until they died or reached the end of the study follow-up period, whichever occurred first. In the secondary analysis, subgroup of dialyzed patients were used and these patients contributed person-time beginning from the date of dialysis initiation until they died or reached the end of the study follow-up period.

**Statistical analysis**

*Effect of dialysis on death*

An extended Cox proportional hazards model with time-varying covariate was used to evaluate hazard of death in elderly and non-elderly patients, allowing for the effect of time-dependent exposure dialysis. Patients contributed time in the unexposed (pre-dialyzed) group until they receive dialysis, death or end of study, whichever occurred first. Patients who received dialysis will begin to contribute time in the exposed (dialyzed) group once dialysis was initiated. In other

words, 'wait time' accrued by a dialyzed patient before receiving dialysis was considered person-time contributed in the unexposed or pre-dialyzed group. Crude survival in pre- and post-dialysis was displayed using Kaplan-Meier survival curves and the difference between the groups was assessed using a log-rank test. The adjusted analysis was controlled for baseline covariates listed above. Proportional hazards assumption was assessed by Schoenfeld residuals plots.

*Factors associated with death in dialyzed patients*

Cox proportional hazards model was used to assess factors associated with death among dialyzed patients across strata of age group (<65 and ≥65 years old). The model included the covariates listed above and two additional covariates – wait time before dialysis initiation and type of dialysis modality. It was important to adjust for wait time before dialysis initiation as patients who initiated dialysis later may have deteriorated more than patients who initiated dialysis earlier. Age was taken to be age at dialysis initiation.

All statistical analyses were Stata, version 11 (StataCorp, College Station, TX). All p values were two-sided and p values of <0.05 were considered statistically significant.

RESULTS

A total of 3990 incident ESRD patients from 44 public dialysis centers were included in the analysis (Figure 1). The characteristics of the patients are shown in Table 1. During the follow-up period, 2799 (70.2%) patients initiated dialysis, 2205 (78.8%) with hemodialysis (HD) while the remaining 594 (21.2%) with peritoneal dialysis (PD) (Figure 2). The total pre-dialyzed person-time for all patients was 3729 person-years (Table 2). Of these, 1128.1 person-years were contributed by dialyzed patients before they began dialysis. After initiating dialysis, the dialyzed patients contributed a total of 12235.7 dialyzed person-years. At the end of study follow-up there was a

total of 2635 deaths. Among those who had initiated dialysis, 1668 (59.6%) died by the end of the study period. As for those who had not initiated dialysis, 967 (81.2%) did not survive past the study period.

*Effect of dialysis on death outcome*

Dialysis significantly reduced hazard of death in elderly and non-elderly patients in both adjusted and unadjusted analysis (Table 3). In the crude Kaplan-Meier analysis, pre-dialysis ESRD patients showed significantly lower survival compared to their dialyzed counterparts ($p < 0.001$) (Figure 3). Median survival time for pre-dialyzed, hemodialysis and peritoneal dialysis were estimated to be 2.72 years (95% CI 2.21, 3.27), 5.52 years (95% CI 5.24, 5.83) and 4.38 years (95% CI 3.72, 4.68), respectively.

When looked by modality of dialysis, patients who initiated with hemodialysis had a significantly lower hazard of death compared to no dialysis in both adjusted and unadjusted analysis (Table 4). When we looked at the stratified analysis by age groups, the elderly had a statistically significantly lower hazard of death for both HD and PD compared to no dialysis (HR 0.530, 95% CI 0.446, 0.629 and HR 0.781, 95% CI 0.624, 0.977, respectively). However, among the non-elderly, HD offered a statistically significantly reduced hazard of death (HR 0.712, 95% CI 0.636, 0.796) but PD did not, albeit not significant (HR 1.004, 95% CI 0.866, 1.165).

*Factors associated with death in dialyzed patients*

In non-elderly dialyzed patients, age at dialysis initiation, peritoneal dialysis, diabetes mellitus, ischemic heart disease and congestive cardiac failure were significantly associated with increased hazard of death while female gender and higher income were associated with a decreased hazard (Table 5). In the elderly, age at dialysis initiation, peritoneal dialysis, current smoking, diabetes mellitus and eGFR <10 ml/min/1.73m$^2$ significantly increased hazard of death. In this group, the

Chinese had a decreased the hazard of death (HR 0.789, 95% CI 0.637, 0.976) compared to Malays. Hypertension was also associated with a decreased hazard of death (HR 0.590, 95% CI 0.448, 0.779, respectively).

## DISCUSSION

This is the first population-based study in Malaysia that follows incident ESRD patients from pre- to post-dialysis and comparing the hazard of death of commencing dialysis among the elderly and non-elderly. Patients aged 65 years and above were defined as elderly as per widely accepted definition of geriatrics.

We found dialysis to be protective in all patients. However, we found that the protection was larger in the elderly and they benefited from both HD and PD while the younger patients only benefited from HD. Even after adjusting for comorbidities, the protective effects of dialysis did not change in the elderly. Patients who commenced dialysis were generally younger, Chinese, had higher education and income and never smoked. Among dialyzed patients, those who had initiated with PD on day one of dialysis had a higher hazard of death compared to those who had initiated with HD. This was true for both elderly and non-elderly. We found dialyzed patients aged 65 years and above with baseline hypertension to have lower hazard of death compared to those without hypertension. The opposite effect was observed among dialyzed patients below 65 years old but the association was not statistically significant.

### *Previous studies*

Our finding was inconsistent with some studies which found the survival advantage of dialysis to have disappeared in the elderly (10) or in the elderly with high comorbidities (9,11). It is

possible that this discrepancy may be due to age differences of our study population. We considered patients aged 65 years and above to be elderly while these studies analyzed much older groups aged 75 and 80 years and above.

With regards to mortality risks in HD compared to PD, the literature have yielded conflicting results. In the elderly aged 65 years and above, a U.S. national cohort study found no significant difference in survival between PD and HD (14). Other population studies on the other hand, found higher risks of death in PD compared to HD in the elderly (15–17).

In another study in Netherlands, it was observed that an initial protective effect was conferred by PD but that reversed with time. The study found that initiating dialysis with PD conferred a 30% lower risk of mortality compared to initiating dialysis with HD (18). However, the relative survival benefit of PD against HD diminished when the risk was observed over time by age groups and diabetes mellitus status. In fact, the authors found that among those aged above 50 years, dialyzing with PD beyond a period of 15 months increased the patients' hazard of death compared to if they had dialyzed with HD. A similar finding was also seen in another study which found that PD was associated with higher hazard of death after one year of follow up, however it was only observed for those aged below 65 years (14).

It is possible that the discrepancies with survival of PD compared to HD that we saw in our study and in other studies may have been attributed to how dialysis initiation date and modality was defined. In this study, we regarded dialysis initiation date to be day one of dialysis and modality type to be the dialysis modality received on this day. Other studies have adopted different definitions. Some studies have taken dialysis initiation date and modality to be that at day 91 or at week 4 after the first dialysis was initiated. This would allow for changes in dialysis modality and patients who died during this period would not be included in the study. Since we were more interested in deciding the modality to start the patient on, we decided to take the modality to be

the type the patient was initiated with on day one. We did not have information on future switches in dialysis modality and did not consider it for this study as we believe changes in modality are usually due to technique failure or other reasons clinicians have little control of.

Studies have shown paradoxical relationship between hypertension and mortality in dialysis patients. A long-term population-based study in Taiwan found higher survival rate in patients with baseline hypertension (19). We saw the same effect in our cohort aged 65 years old and above. However, in those aged less than 65 years old, a reversed, albeit non-significant, effect was seen, suggesting possible effect modification by age.

The logic behind the protective effect of hypertension possibly has to do with pre-dialytic or intradialytic blood pressure. It has been postulated that the relationship between systolic blood pressure (SBP) and mortality in older patients is an L-shaped curve, suggesting increased mortality at lower SBP values (20). In younger patients, however, the relationship is a reverse L-shaped curve.

However, in a systematic review it was suggested that lowering blood pressure with anti-hypertensive agents can reduce cardiovascular morbidity and mortality in dialyzed patients regardless of age (21). Nevertheless, this goes against nephrologists' general reluctance in giving hypertensives for the reason that it may cause intradialytic hypotension and possibly lead to cardiovascular complications and death (22). Another possible explanation for the difference we saw between the elderly and non-elderly could be due to choice of anti-hypertensives in younger and older hypertensive patients. Unfortunately, we did not have information on prescriptions of these patients to investigate this.

*Strengths and limitations*

Our study has several strengths. First, our cohort consist of incident ESRD patients followed from the day of diagnosis for dialysis initiation status and mortality outcomes. Other studies had observed patients that were already on dialysis or CKD patients that have not reached ESRD yet. Thus, our study was better able to quantify hazards of death among patients that have already reach ESRD but not necessarily on dialysis.

Secondly, our analysis was designed to avoid immortal time bias. Studies where a patient's exposure status can change during the follow up are susceptible to immortal time bias if not corrected for. In our cohort, all patients initially entered the study as pre-dialyzed patients and over time, some of these patients commenced dialysis while others did not. Classifying a patient's time in the study as exposed or unexposed based solely on dialysis status with no regard to when dialysis was initiated would create immortal time bias. This is because for those who eventually commenced dialysis, the time between cohort entry and dialysis initiation were 'immortal' because the patient necessarily had to remain alive until dialysis was initiated. To avoid this, we regarded time contributed by a patient before commencing dialysis to be unexposed person-time while time after commencing dialysis as exposed person-time and used a Cox proportional hazards model extended to allow for the time-dependent exposure.

Thirdly, we accounted for wait time before dialysis initiation in our analysis of hazard of death among dialyzed patients. Many patients in our cohort did not begin dialysis immediately after diagnosis of ESRD. Patients who have waited for substantial periods of time before commencing dialysis may have deteriorated more than other who had dialyzed earlier. Thus, accounting for this differences may give better estimates.

Our study is limited by possible competing risk bias. In determining hazard of death by dialysis modality, patients who initiate HD would not initiate PD and vice versa and the choice of whether a patient initiates with HD or PD may be related to the outcome. Thus, this could potentially result in selection bias.

Additionally, our data did not observe changes in dialysis modality over time. We treated the dialysis modality at initiation to be the modality the patient was on for the entire duration of the study. Therefore our study was not able to show if changes in dialysis modality and its direction of change had any effect on mortality risks. Nevertheless, it is interesting to note that the risk of death in PD compared to HD had been attenuated over the years. This was shown in studies in U.S. and Europe which compared cohorts of patients who initiated dialysis at different years. The studies saw higher risks of death among patients who initiated PD in the 1990s, however the risks were lowered for later cohorts (23,24). Furthermore, the study from Europe found survival on PD to be better than HD among the cohort that initiated dialysis between years 2003-2007 for patients younger than 65 years old and for non-diabetics (24).

*Future research*

In Malaysia, PD death rate has been higher than HD since 2006. Given that changes in mortality risks for PD have been observed with time in US and Europe, it would be interesting to study if a similar trend will be observed in the Malaysian population. Furthermore, it would also be interesting to investigate effects of changes in modality and types of anti-hypertensives used. Therefore a longitudinal study following patients over time for changes in modality, hypertension status, types of anti-hypertensive medications used and pre-dialysis and intradialysis blood pressure will be beneficial.

## CONCLUSION

Dialysis improves survival in ESRD patients in both elderly and non-elderly. Starting an elderly ESRD patient with dialysis regardless of modality would improve their survival however, PD showed a higher risk of mortality compared to HD.

REFERENCES


1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Lond Engl. 2017 Sep 16;390(10100):1211–59.

2. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PloS One. 2016;11(7):e0158765.

3. Ageing and health [Internet]. [cited 2019 Mar 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

4. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Lond Engl. 2017 Sep 16;390(10100):1151–210.

5. Hooi LS, Ong LM, Ahmad G, Bavanandan S, Ahmad NA, Naidu BM, et al. A population-based study measuring the prevalence of chronic kidney disease among adults in West Malaysia. Kidney Int. 2013 Nov;84(5):1034–40.

6. 24th Report of the Malaysian Dialysis and Transplant Registry 2016. National Renal Registry;

7. Bujang MA, Adnan TH, Hashim NH, Mohan K, Kim Liong A, Ahmad G, et al. Forecasting the Incidence and Prevalence of Patients with End-Stage Renal Disease in Malaysia up to the Year 2040. Int J Nephrol. 2017;2017:2735296.

8. Noble H, Meyer J, Bridges J, Kelly D, Johnson B. Reasons Renal Patients Give for Deciding Not to Dialyze: A Prospective Qualitative Interview Study. Dial Transplant. 2009;38(3):82–9.

9. Murtagh FEM, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2007 Jul;22(7):1955–62.

10. Chandna SM, Da Silva-Gane M, Marshall C, Warwicker P, Greenwood RN, Farrington K. Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2011 May;26(5):1608–14.

11. Hussain JA, Mooney A, Russon L. Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. Palliat Med. 2013 Oct;27(9):829–39.

12. Chiu Y-L, Chien K-L, Lin S-L, Chen Y-M, Tsai T-J, Wu K-D. Outcomes of stage 3-5 chronic kidney disease before end-stage renal disease at a single center in Taiwan. Nephron Clin Pract. 2008;109(3):c109-118.

13. Lai X, Zhang A-H, Chen S-Y, He L, Su C-Y, Fan M-H, et al. Outcomes of stage 1-5 chronic kidney disease in Mainland China. Ren Fail. 2014 May;36(4):520–5.

14. Jaar BG, Coresh J, Plantinga LC, Fink NE, Klag MJ, Levey AS, et al. Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. Ann Intern Med. 2005 Aug 2;143(3):174–83.

15. Collins AJ, Weinhandl E, Snyder JJ, Chen S-C, Gilbertson D. Comparison and survival of hemodialysis and peritoneal dialysis in the elderly. Semin Dial. 2002 Apr;15(2):98–102.

16. Winkelmayer WC, Glynn RJ, Mittleman MA, Levin R, Pliskin JS, Avorn J. Comparing mortality of elderly patients on hemodialysis versus peritoneal dialysis: a propensity score approach. J Am Soc Nephrol JASN. 2002 Sep;13(9):2353–62.

17. Lee S, Ryu J-H, Kim H, Kim KH, Ahn HS, Hann HJ, et al. An assessment of survival among Korean elderly patients initiating dialysis: a national population-based study. PloS One. 2014;9(1):e86776.

18. Liem YS, Wong JB, Hunink MGM, de Charro FT, Winkelmayer WC. Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands. Kidney Int. 2007 Jan;71(2):153–8.

19. Chien C-C, Yen C-S, Wang J-J, Chen H-A, Chou M-T, Chu C-C, et al. Reverse epidemiology of hypertension-mortality associations in hemodialysis patients: a long-term population-based study. Am J Hypertens. 2012 Aug;25(8):900–6.

20. Myers OB, Adams C, Rohrscheib MR, Servilla KS, Miskulin D, Bedrick EJ, et al. Age, race, diabetes, blood pressure, and mortality among hemodialysis patients. J Am Soc Nephrol JASN. 2010 Nov;21(11):1970–8.

21. Heerspink HJL, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE, Jardine MJ, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. Lancet Lond Engl. 2009 Mar 21;373(9668):1009–15.

22. Tomson CRV. Blood pressure and outcome in patients on dialysis. Lancet Lond Engl. 2009 Mar 21;373(9668):981–2.

23. Mehrotra R, Chiu Y-W, Kalantar-Zadeh K, Bargman J, Vonesh E. Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. Arch Intern Med. 2011 Jan 24;171(2):110–8.

24. van de Luijtgaarden MWM, Jager KJ, Segelmark M, Pascual J, Collart F, Hemke AC, et al. Trends in dialysis modality choice and related patient survival in the ERA-EDTA Registry over a 20-year period. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2016 Jan;31(1):120–8.

TABLES AND FIGURES

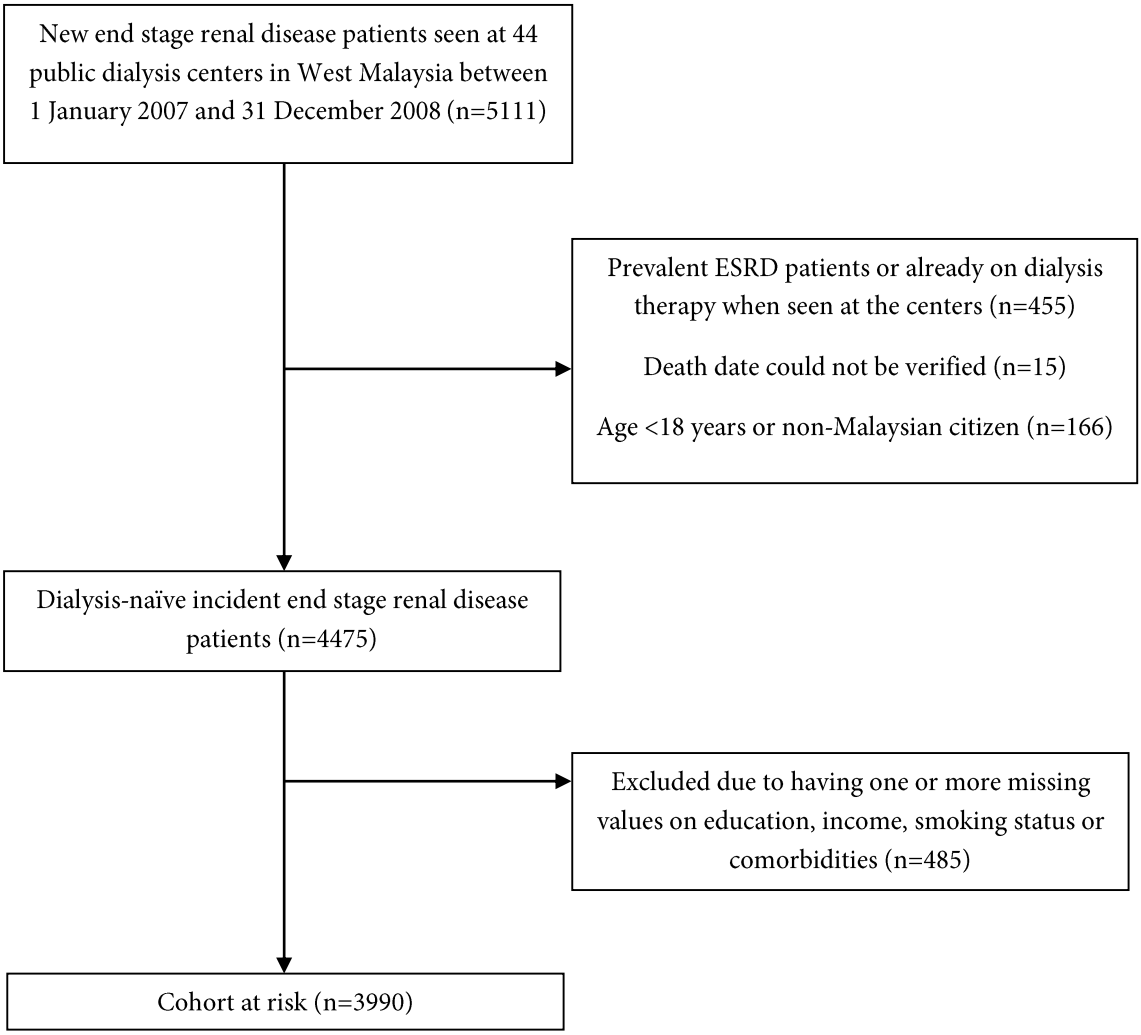



Figure 1. Flowchart of patient inclusion and exclusion

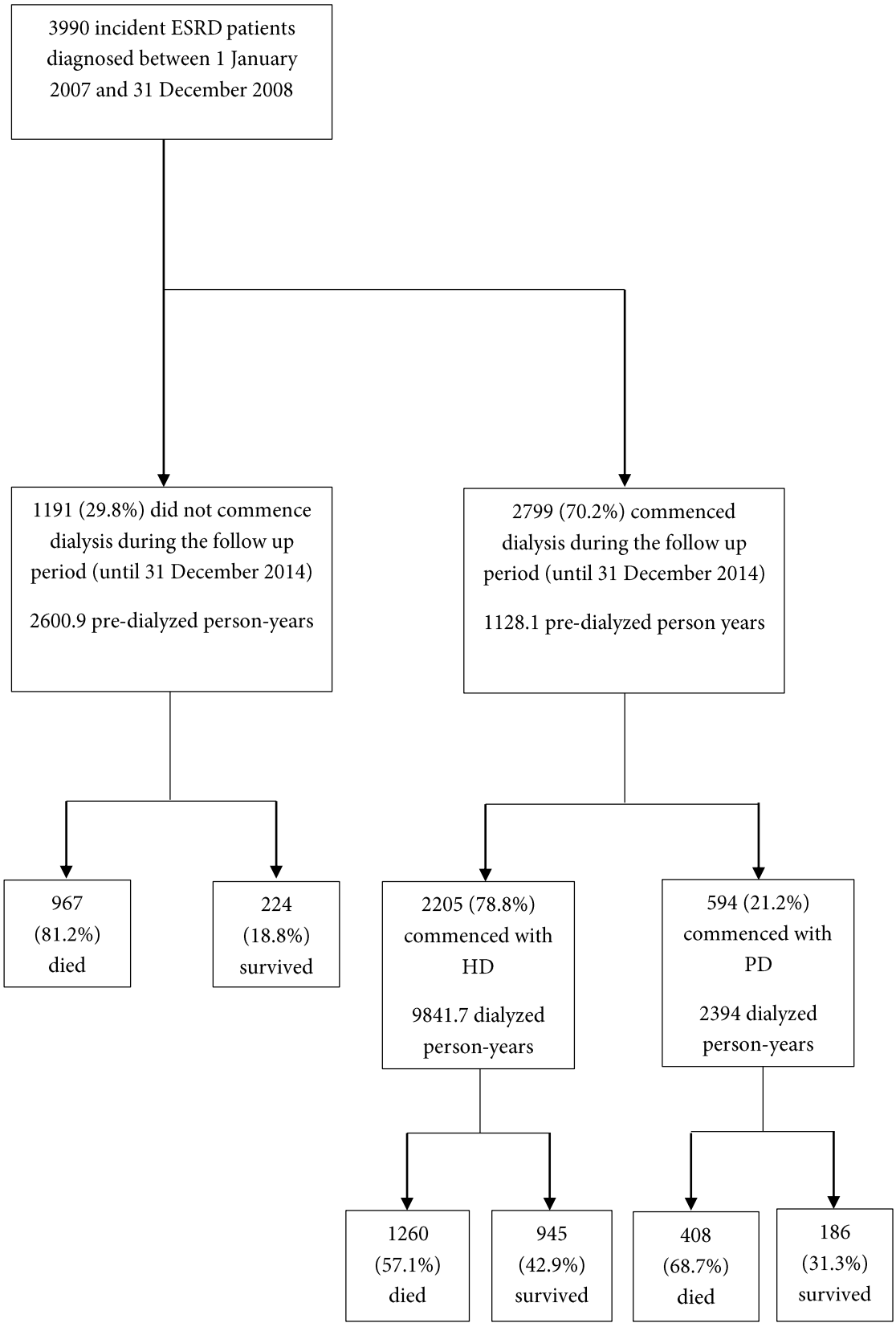
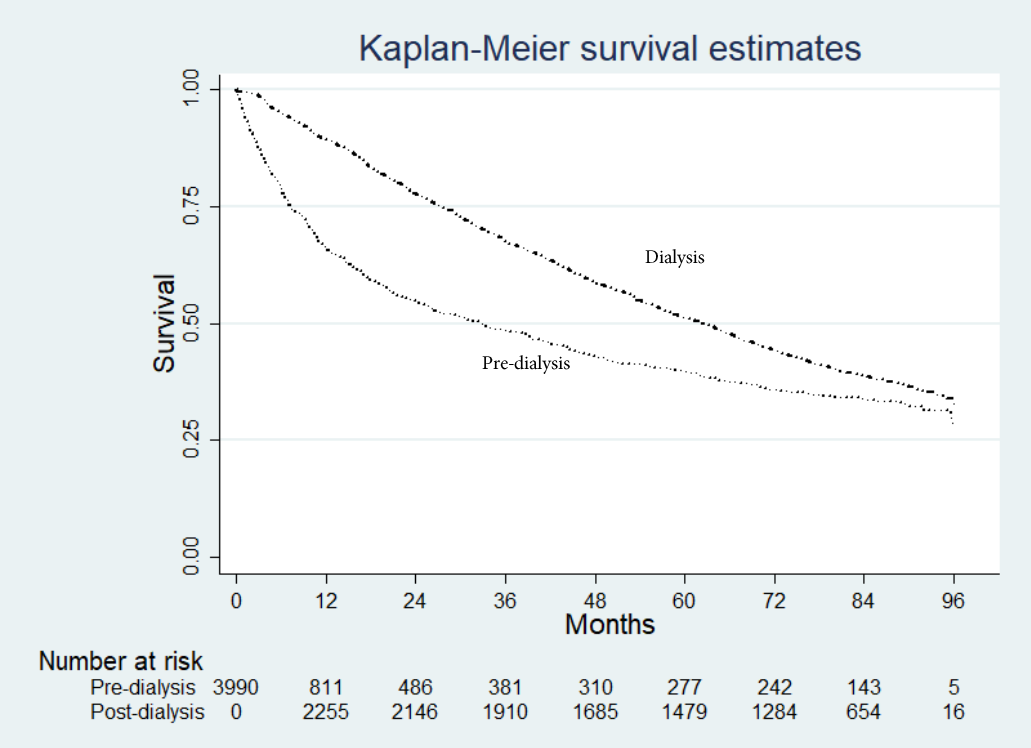



Figure 2. Patient follow-up

a)




b)

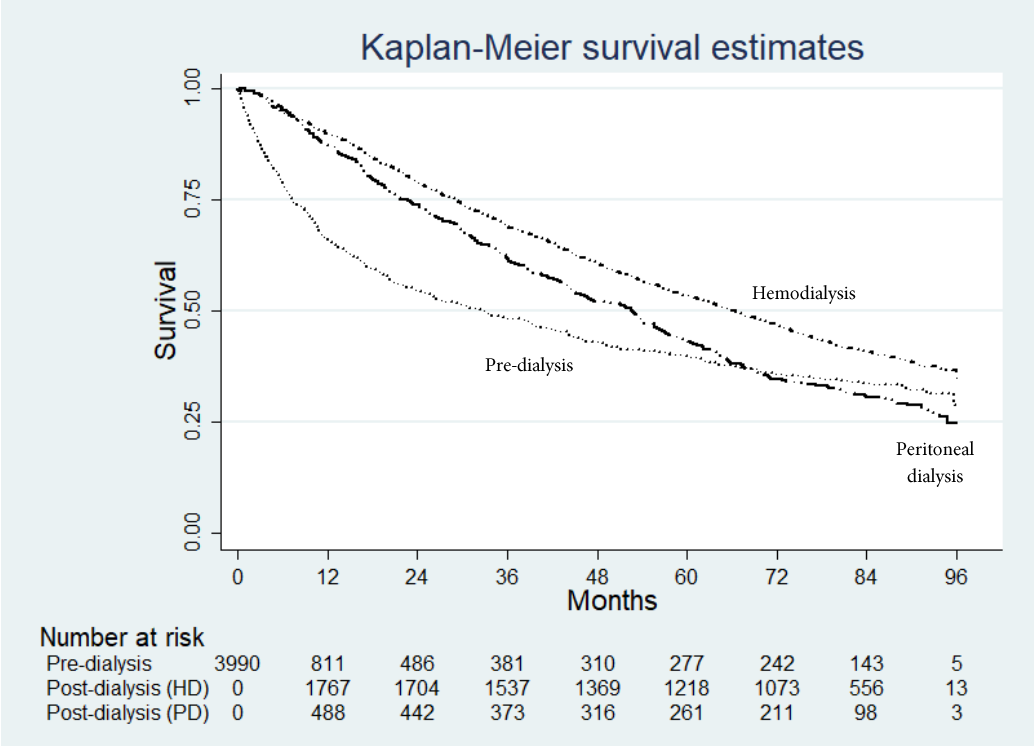



Figure 3. a) Kaplan-Meier survival curves for all-cause mortality by dialysis status; b) Kaplan-Meier survival curves for all-cause mortality by dialysis status and modality

Table 1. Characteristics of pre-dialyzed ESRD patients and a subgroup of patients who eventually received dialysis by dialysis modality[a]

| **Characteristics** | **Incident ESRD, n=3990** | **Dialyzed, n=2799** | |
|---|---|---|---|
| | | **Hemodialysis, n=2205** | **Peritoneal dialysis, n=594** |
| Age at ESRD diagnosis (years), mean (SD) | 55.7 (12.9) | 54.4 (12.4) | 54.1 (14.0) |
| Gender, n (%) | | | |
| Male | 2125 (53.3) | 1187 (53.8) | 300 (50.5) |
| Female | 1865 (46.7) | 1018 (46.2) | 294 (49.5) |
| Race, n (%) | | | |
| Malay | 2657 (66.6) | 1431 (64.9) | 368 (62.0) |
| Chinese | 939 (23.5) | 551 (25.0) | 172 (29.0) |
| Indian | 374 (9.4) | 210 (9.5) | 51 (8.6) |
| Others | 20 (0.5) | 13 (0.6) | 3 (0.5) |
| Education, n (%) | | | |
| Nil | 467 (11.7) | 227 (10.3) | 50 (8.4) |
| Primary | 1683 (42.2) | 872 (39.6) | 251 (42.3) |
| Secondary | 1683 (42.2) | 999 (45.3) | 265 (44.6) |
| Tertiary | 157 (3.9) | 107 (4.9) | 28 (4.7) |
| Income[b], n (%) | | | |

| | | | |
|---|---|---|---|
| <RM 1000 | 1920 (48.1) | 1030 (46.7) | 221 (37.2) |
| RM 1000-3000 | 1435 (36.0) | 805 (39.5) | 259 (43.6) |
| RM 3001-5000 | 456 (11.4) | 260 (11.8) | 90 (15.2) |
| RM 5001-10000 | 179 (4.5) | 110 (5.0) | 24 (4.0) |
| Smoking, n (%) | | | |
| Never smoked | 2744 (68.8) | 1534 (69.6) | 434 (73.1) |
| Former smoker | 1001 (25.1) | 534 (24.2) | 126 (21.2) |
| Current smoker | 245 (6.1) | 137 (6.2) | 34 (5.7) |
| Diabetes mellitus, n (%) | 2099 (52.6) | 1182 (53.6) | 286 (48.2) |
| Hypertension, n (%) | 3440 (86.2) | 1935 (87.8) | 515 (86.7) |
| Ischemic heart disease, n (%) | 632 (15.8) | 300 (13.6) | 105 (17.7) |
| Congestive cardiac failure, n (%) | 216 (5.4) | 105 (4.8) | 28 (4.7) |
| Glomerular filtration rate, n (%) | | | |
| >=10 ml/min/1.73m$^2$ | 1510 (37.8) | 840 (38.1) | 203 (34.2) |
| <10 ml/min/1.73m$^2$ | 2480 (62.2) | 1365 (61.9) | 391 (65.8) |

*ESRD* end stage renal disease, *SD* standard deviation

[a] The total cohort comprised of incident ESRD patients. Dialyzed patients were a subgroup of these patients who started dialysis during the follow-up period between 1 January 2007 and 31 December 2008.

[b] Exchange rate at the time of writing: USD 1 = RM 4.10

Table 2. Mortality and person-years accrued by dialysis status and dialysis modality

| | **Pre-dialysis** | **Dialysis** | **Hemodialysis** | **Peritoneal dialysis** |
|---|---|---|---|---|
| N | 3990 | 2799 | 2205 | 594 |
| Total person-years accrued[a] | 3729.0 | 12235.7 | 9841.7 | 2394.0 |
| Years in study, mean (SD) | 2.18 (2.74)[b] | 4.37 (2.44) | 4.46 (2.40) | 4.03 (2.43) |
| Years in study, median (25$^{th}$, 75$^{th}$ percentile) | 0.70 (0.19, 3.68)[b] | 4.75 (2.11, 6.50) | 5.00 (2.25, 6.55) | 4.04 (1.82, 6.33) |
| Deaths, n (%) | 967 (81.2)[b] | 1668 (59.6) | 1260 (57.1) | 408 (68.7) |

*SD* standard deviation

Note: The cohort entered the study as pre-dialyzed ESRD patients (n=3990). Some of these patients commenced dialysis, either with hemodialysis or with peritoneal dialysis, while some remained un-dialyzed.

[a] Total person-years accrued refers to the total number of years the patients contributed based on their status. Total person-years accrued for pre-dialysis includes the total person-years contributed by dialyzed patients before they commenced dialysis

[b] This shows the mean and median years in study and proportion died among those who were still not dialyzed at the end of the study only (n=1191)

Table 3. Unadjusted and adjusted hazard ratios[a] for death in dialyzed compared to pre-dialyzed patients stratified by age group[b]

| | Proportion died | Unadjusted HR (95% CI) | p-value | Adjusted[c] HR (95% CI) | p-value |
|---|---|---|---|---|---|
| All patients | 2635/3990 | 0.656 (0.602, 0.716) | <0.001 | 0.719 (0.659, 0.786) | <0.001 |
| Age at ESRD diagnosis | | | | | |
| Age <65 years | 1836/3033 | 0.730 (0.656, 0.812) | <0.001 | 0.763 (0.685, 0.850) | <0.001 |
| Age ≥65 years | 799/957 | 0.554 (0.474, 0.646) | <0.001 | 0.582 (0.495, 0.684) | <0.001 |

*ESRD* end stage renal disease, *HR* hazard ratio, *CI* confidence interval

[a] Extended Cox proportional hazards regression with dialysis as time-dependent exposure variable

[b] Non-dialyzed as the reference level

[c] Adjusted for age, gender, race, education level, income level, smoking status, diabetes mellitus status, hypertension status, ischemic heart disease status, congestive cardiac failure status and glomerular filtration rate level

Table 4. Unadjusted and adjusted hazard ratios[a] for death in hemodialysis and peritoneal dialysis stratified by age group[b]

| | Unadjusted HR (95% CI) | | | | Adjusted[c] HR (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | **HD** | **p-value** | **PD** | **p-value** | **HD** | **p-value** | **PD** | **p-value** |
| All patients, n=3990 | 0.617 (0.563, 0.676) | <0.001 | 0.810 (0.718, 0.914) | <0.001 | 0.667 (0.608, 0.731) | <0.001 | 0.948 (0.839, 1.072) | 0.397 |
| Age at ESRD diagnosis | | | | | | | | |
| Age <65 years, n=3033 | 0.694 (0.621, 0.775) | <0.001 | 0.877 (0.757, 1.015) | 0.078 | 0.712 (0.636, 0.796) | <0.001 | 1.004 (0.866, 1.165) | 0.954 |
| Age ≥65 years, n=957 | 0.509 (0.431, 0.601) | <0.001 | 0.710 (0.572, 0.881) | 0.002 | 0.530 (0.446, 0.629) | <0.001 | 0.781 (0.624, 0.977) | 0.031 |

*ESRD* end stage renal disease, *HR* hazard ratio, *CI* confidence interval

[a] Extended Cox proportional hazards regression with dialysis as time-dependent exposure variable

[b] Non-dialyzed as the reference level

[c] Adjusted for age, gender, race, education level, income level, smoking status, diabetes mellitus status, hypertension status, ischemic heart disease status, congestive cardiac failure status and glomerular filtration rate level

Table 5. Predictors of death in dialyzed patients stratified by age at dialysis initiation

| | **Age <65 years at dialysis initiation (n=2194)** | | | | **Age ≥65 years at dialysis initiation (n=605)** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Unadjusted HR (95% CI)** | **p-value** | **Adjusted[a] HR (95% CI)** | **p-value** | **Unadjusted HR (95% CI)** | **p-value** | **Adjusted[a] HR (95% CI)** | **p-value** |
| Wait time (years) | 0.935 (0.837, 1.044) | 0.233 | 0.974 (0.869, 1.092) | 0.447 | 0.953 (0.834, 1.089) | 0.479 | 0.979 (0.856, 1.120) | 0.760 |
| Age at dialysis initiation (years) | 1.039 (1.033, 1.045) | <0.001 | 1.031 (1.023, 1.038) | <0.001 | 1.019 (0.998, 1.040) | 0.078 | 1.025 (1.004, 1.047) | 0.022 |
| Dialysis modality | | | | | | | | |
| Hemodialysis | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Peritoneal dialysis | 1.276 (1.117, 1.458) | <0.001 | 1.449 (1.265, 1.659) | <0.001 | 1.452 (1.182, 1.784) | <0.001 | 1.513 (1.219, 1.878) | <0.001 |
| Gender | | | | | | | | |
| Male | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Female | 0.821 (0.733, 0.920) | <0.001 | 0.812 (0.704, 0.936) | 0.004 | 0.958 (0.797, 1.152) | 0.650 | 1.009 (0.798, 1.275) | 0.941 |
| Race | | | | | | | | |
| Malay | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Chinese | 1.025 (0.895, 1.174) | 0.724 | 0.960 (0.837, 1.103) | 0.566 | 0.793 (0.102, 5.194) | 0.023 | 0.789 (0.637, 0.976) | 0.029 |
| Indian | 1.206 (1.001, 1.453) | 0.048 | 1.146 (0.948, 1.385) | 0.158 | 1.100 (0.782, 1.546) | 0.584 | 1.051 (0.740, 1.493) | 0.780 |
| Others | 0.516 (0.214, 1.243) | 0.140 | 0.646 (0.267, 1.561) | 0.332 | 0.729 (0.102, 5.194) | 0.752 | 1.087 (0.148, 7.992) | 0.935 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Education | | | | | | | | |
| Nil | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Primary | 0.805 (0.653, 0.994) | 0.044 | 0.854 (0.689, 1.058) | 0.149 | 1.130 (0.888, 1.438) | 0.322 | 1.201 (0.930, 1.549) | 0.160 |
| Secondary | 0.638 (0.518, 0.784) | <0.001 | 0.865 (0.691, 1.083) | 0.207 | 1.049 (0.792, 1.390) | 0.736 | 1.021 (0.738, 1.414) | 0.899 |
| Tertiary | 0.470 (0.337, 0.655) | <0.001 | 0.774 (0.538, 1.114) | 0.169 | 1.135 (0.572, 2.253) | 0.717 | 0.967 (0.446, 2.098) | 0.933 |
| Income[b] | | | | | | | | |
| <RM 1000 | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| RM 1000-3000 | 0.834 (0.738, 0.943) | 0.004 | 0.850 (0.750, 0.964) | 0.011 | 1.015 (0.827, 1.245) | 0.890 | 1.021 (0.819, 1.274) | 0.852 |
| RM 3001-5000 | 0.712 (0.587, 0.863) | <0.001 | 0.750 (0.614, 0.917) | 0.005 | 1.048 (0.793, 1.385) | 0.741 | 1.088 (0.811, 1.459) | 0.573 |
| RM 5001-10000 | 0.652 (0.489, 0.870) | 0.004 | 0.651 (0.480, 0.883) | 0.006 | 1.087 (0.671, 1.761) | 0.736 | 1.241 (0.718, 2.148) | 0.439 |
| Smoking | | | | | | | | |
| Never smoked | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Former smoker | 1.171 (1.027, 1.334) | 0.018 | 1.008 (0.865, 1.175) | 0.921 | 1.148 (0.926, 1.422) | 0.208 | 1.114 (0.866, 1.432) | 0.402 |
| Current smoker | 1.143 (0.918, 1.425) | 0.233 | 1.137 (0.897, 1.441) | 0.288 | 1.646 (1.057, 2.564) | 0.027 | 1.646 (1.017, 2.662) | 0.043 |
| Diabetes mellitus | 2.025 (1.800, 2.278) | <0.001 | 1.627 (1.437, 1.841) | <0.001 | 1.272 (1.056, 1.531) | 0.011 | 1.320 (1.077, 1.619) | 0.008 |
| Hypertension | 1.257 (1.049, 1.506) | 0.013 | 1.070 (0.891, 1.284) | 0.468 | 0.670 (0.515, 0.872) | 0.003 | 0.591 (0.448, 0.780) | <0.001 |
| Ischemic heart disease | 1.883 (1.624, 2.183) | <0.001 | 1.359 (1.165, 1.584) | <0.001 | 1.341 (1.078, 1.669) | 0.008 | 1.210 (0.958, 1.526) | 0.109 |
| Congestive cardiac failure | 1.708 (1.322, 2.205) | <0.001 | 1.393 (1.073, 1.808) | 0.013 | 1.259 (0.916, 1.731) | 0.156 | 1.169 (0.837, 1.632) | 0.360 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Glomerular filtration rate | | | | | | | | |
| >=10 ml/min/1.73m$^2$ | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| <10 ml/min/1.73m$^2$ | 0.994 (0.885, 1.117) | 0.922 | 0.976 (0.866, 1.099) | 0.686 | 1.203 (0.995, 1.456) | 0.057 | 1.225 (1.003, 1.496) | 0.047 |

*HR* hazard ratio, *CI* confidence interval

[a] Adjusted for wait time to dialysis, age at dialysis initiation, dialysis modality, gender, race, education level, income level, smoking status, diabetes mellitus status, hypertension status, ischemic heart disease status, congestive cardiac failure status and glomerular filtration rate level

[b] Exchange rate at the time of writing: USD 1 = RM 4.10