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Predictive Factors of First-Year Mortality in Newly Diagnosed End-Stage Renal Disease Patients Commencing on Hemodialysis in Kelantan, Malaysia

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Abstract

Background: Globally the number of End-stage renal disease (ESRD) patients has been increasing in trend both developed and developing countries, worldwide. The annual death rate for ESRD on hemodialysis (HD) in Malaysia 2015 was 13.8%. The overall 5 years and 10 years of survival on dialysis were 52% and 27% respectively. The trend for death rate among HD patients had gradually increased over the past 2 decades. Dialysis has a massive impact on financial resources and utilization. The highest incidence of mortality is found to be during the first year of initiation of hemodialysis. Several studies have comprehensively analyzed various existing risk factors during the pre-dialysis stage associated with first-year mortality after commencing HD; however, the results were inconsistent due to lack of local data. This study was carried out to identify prognostic factors that contribute to the first-year mortality in newly diagnosed ESRD patients in the state of Kelantan, Malaysia.

Method: A prospective cohort study was conducted involving 373 ESRD patients newly initiated hemodialysis from 28 hemodialysis center in Kelantan from 1st January 2016 to 31st December 2016. Follow up of one year after recruitment of the subjects was done until 31st December 2017. All patients who fulfilled the criteria were included in the study. The required information on variables of interest was taken every 3 months during blood taking and recorded in ADNAN (Advanced Dialysis Nephrology Application) system. The survival status until 31st December 2017 was recorded into a data collection form.

Results: The overall cumulative survival of ESRD during the first-year initiation on HD in Kelantan was 89.5 (95% CI 86.5, 92.7) percent.

Based on Cox Proportional Hazards Regression multivariable analysis after adjusting other variables, the significant prognostic factors that influenced the risk of mortality in ESRD patients during first-year of initiation of hemodialysis were female gender (HR=2.40, 95% CI: 1.23, 4.69) and serum albumin less than 30 g/l (HR=0.93, 95% CI: 0.89, 0.98).

Conclusion: The survival rate of ESRD patients during the first-year initiation of HD in Kelantan was comparable with other developed countries. Significant independent prognostic factors identified were considered similar to other countries.

Keywords: End-stage renal disease; Hemodialysis; First-year; Incident hemodialysis; Survival; Prognostic factor

Abbreviations

ESRD: End Stage Renal Disease; RRT: Renal Replacement Therapy; GFR: Glomerular Filtration Rate; pmp: per million population; HD: Hemodialysis; DM: Diabetes Mellitus; HPT: Hypertension; ADNAN: Advanced Dialysis Nephrology Application Network; HDU: Hemodialysis Unit; ALP: Alkaline phosphatase; iPTH: intact parathyroid hormone

Introduction

Globally the number of ESRD patients has been increasing in trend both developed and

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developing countries, worldwide. The incidence of ESRD in Malaysia has been an increase in trend for the past 10 years. In 2001 there were 88 per million populations (pmp) and this had doubled to 170pmp in 2010. Meanwhile, the prevalence of patients with ESRD on dialysis had doubled from 562pmp in 2006 to 1220pmp in 2015 [1]. Current projections indicate that, by 2030, the global population of ESRD patients living on dialysis may exceed 2 million [1]. Dialysis has a massive impact on financial resources and utilization.

The annual death rate for ESRD on hemodialysis (HD) in 2015 was 13.8%. The overall 5 years and 10 years of survival on dialysis were 52% and 27% respectively [1]. The trend for death rate among HD patients had gradually increased over the past 2 decades.

The prognosis of the patient with ESRD remains poor even though there had been many advances in the treatment; therefore identification of risk factors which predispose to mortality is important. With early identification of the risk factors, the morbidity and mortality of these patients going for HD will be reduced in the future.

One of the risk factors associated with deterioration of renal function is cardiovascular disease. This factor is more predominant in the patient when they were initiated on dialysis. Based on National Registry 2015, cardiovascular disease accounted for 34% of all death. Death at home accounted for another 18% and the majority of this death was attributed to probably cardiovascular events [1].

Therefore, besides treating the modifiable risk factors namely; smoking, diabetes mellitus (DM), hypertension (HPT), and hyperlipidemia, it is also important to treat the non-modifiable risk factors namely iron deficiency, anemia, insulin resistance and also vitamin D deficiency [3-5]. Preventive measures should not only focus on disease prevention, but also in modifying disease outcomes. To improve patient's survival and quality of life on dialysis therapy, it is important to modify these risk factors [6-8].

The risk of mortality among patients on HD is high and it varies among patients. There is no tool that is widely available for use to predict the mortality. Availability of a tool or predictive model which is able to stratify risk of mortality would be helpful for HD centers. This model will be able to classify patients into high, moderate and low risk. With this, dialysis providers can have an overview of types of patients that they are dealing with. This tool can also be used in the future study and help to identify suitable dialysis prescriptions or medications. This will help in providing clinical evidence in our clinical practice. This 'risk-stratification-tool' could either be used as a clinical score or embedded in computer-based management systems.

Data in South East Asia population is also lacking.

Patient variables that have a significant impact on mortality were age, gender, primary renal disease, dialysis modality, body mass index (BMI), diastolic blood pressure and the presence of cardiovascular disease. The biochemical variables associated with a significant risk factor for mortality were serum albumin, serum cholesterol, hemoglobin, calcium, calcium phosphate product, phosphate and hepatitis B status [1].

This study intends to describe the demographic profile of newly diagnosed HD patients within their first year of treatment focusing on mortality among them. It will determine the risk factors associated with early death among the Kelantan population during the first year of dialysis. Risk factors assessed include patient's demography, co-morbidities, and several laboratory parameters. This study will then further analyze the significance of each parameter in relation to one-year mortality.

Determination of these key predictors of early mortality will enable formulation of an effective risk prediction scoring system for clinical use in improving and reducing mortality of ESRD initiated on HD. Careful selection of patients for HD based on a predictive scoring system can improve the mortality rate of HD patients and ensure optimal utilization of public resources.

Besides, this will create an opportunity for intervention for those modifiable risk factors such as HPT, DM, and renal bone chemistry.

Materials and Methods

Design and population

This was a prospective cohort study design involving End Stage Renal Disease subjects who initiated regular hemodialysis in their first year. The study was carried out in all Hemodialysis Unit in both Government and Private in the State of Kelantan from January 2016 to December 2017. We included newly diagnosed End Stage Renal Disease patients who were above the age of 18 years and initiated on hemodialysis between January 2016 to December 2016. Patients who underwent kidney transplant pre-emptively or within one year of hemodialysis, patients with cancer, patients who recovered kidney function within 90 days after initiation of dialysis, patients who switched treatment at any given time were excluded from the study. Patients were follow-up for one year until December 2017.

Data collection

A patient was diagnosed with End Stage Renal Disease and initiated on regular hemodialysis and registered into Advanced Dialysis Nephrology Application Network (ADNAN) system. This system is a database containing all patients undergoing hemodialysis in the state of Kelantan for purpose of efficient medical records in the state of Kelantan, especially during a disaster. Baseline demographics and blood investigations which consist of hemoglobin, albumin, calcium, phosphate, intact parathyroid hormone, and alkaline phosphatase will be entered into the system by the hemodialysis staff in Hemodialysis Unit (HDU) in charge of the patient.

The patient underwent hemodialysis 3 times per week according to schedule. Blood was withdrawn again at 3 months, 6 months, 9 months and 12 months and was entered into ADNAN system. Venous blood taken was also routine blood investigations taken to monitor patient's blood parameters to ensure adequacy of hemodialysis.

Information on these parameters would be retrieved from ADNAN system and recorded in the case report form (CRF). The survival status was ascertained during subject's attendance to hemodialysis center for hemodialysis.

Data analysis

Data entry was performed and analyzed using IBM Statistical Package for Social Sciences (SPSS) version 22.0 Armonk, NY: IBM Corp). Data were checked, explored and cleaned. The distributions and frequencies were examined. Data exploration was done including descriptive statistics and graphs for each variable. All continuous variables were expressed as mean with standard deviation or median with interquartile range. Meanwhile, frequencies and percentages were obtained for categorical variables.

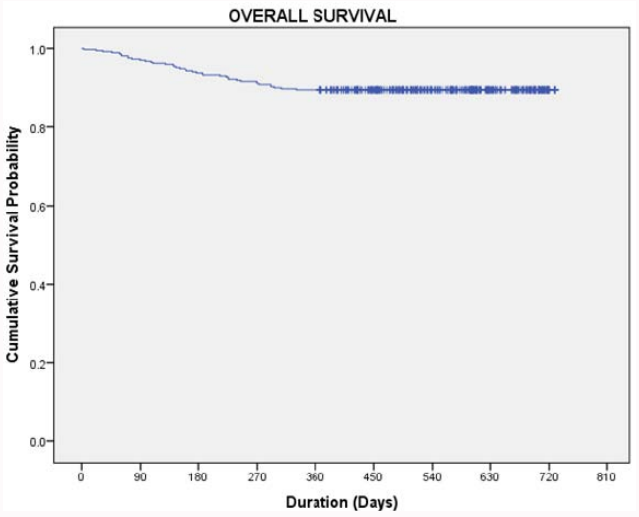

Figure 1: Overall Kaplan Meier survival curve for 373 ESRD patients initiated on hemodialysis in Kelantan.

Patient survival over 1 year based on time to death or last follow up were analyzed using the Kaplan-Meier method and expressed as percentages with 95% confidence intervals. The comparison of survival distributions in all independent variable groups was evaluated using the Log-rank test. Simple Cox's regression analysis was conducted for all independent variables to provide a preliminary idea to which variable had possible prognostic importance. Then, multivariable analysis using Cox Proportional Hazard Regression Model was applied to identify prognostic variables.

Results

A total of 475 patients that were newly registered in 28 hemodialysis center in Kelantan in 2016 were identified from the ADNAN system that later subjected to screening based on the inclusion and exclusion criteria of the study. Out of these only 415 patients were eligible for the inclusion into the study. Another 42 patients have to be discarded due to a large amount of missing data. In the end, only 373 subjects were included in the final statistical analyses.

The mean (standard deviation) age of all patients was 54.9 (14.1) years. The youngest patient aged 18 and the oldest aged 85. According to age group, approximately half (51.2%) of the patients were aged 45 to 64 years old. The female to male ratio was 1:1.

A relatively higher percentage of overall patients had hypertension than diabetes. Percentage of males who had diabetes mellitus and hypertension were greater than females. Similarly, more percentage of males had ischemic heart disease than their counterparts.

The ESRD patients were predominantly having hemoglobin less than 10g/dl during the initiation of HD. About 30 percent of the patients had an albumin level of less than 30g/l during initiation. Surprisingly, more than half of the patients had ALP less than 150U/l, while the majority of patients had a calcium level of normal 2.1 to 2.37 mmol/l, phosphate between 1.3 to 1.8 mmol/l and calcium phosphate product of 3.5 to 4.5 $mmol^2/L^2$.

Patient that passed away within the first-year initiation of hemodialysis had hemoglobin less than 10g/dl, albumin less than 30g/l. Table 1 shows the summary of the baseline clinical characteristics.

The overall survival probability curve for ESRD patients initiated on hemodialysis in Kelantan is represented in Figure 1. The result from Kaplan-Meier analysis and survival function plot show that the cumulative proportion of survival decreases over time. The overall mean survival time was 669 with its 95% confidence interval of 652 to 688 days.

Table 1: Clinical characteristics of 373 patients undergoing hemodialysis in Kelantan.

Clinical characteristics	Entire cohort (n = 373)	First-year mortality (n=39)	Survived >1 year (n=334)
Hemoglobin, g/dl			
<10	293 (78.6)	33 (11.3)	260 (88.7)
10-12	39 (10.5)	5 (12.8)	34 (87.2)
>12	11 (2.9)	1 (9.1)	10 (90.9)
Albumin, g/l			
<30	104 (27.9)	17 (16.3)	87 (83.7)
30-35	97 (26)	10 (10.3)	87 (89.7)
>35	146 (39.1)	11 (7.5)	135 (92.5)
ALP, U/l			
<150	261 (70)	29 (11.1)	232 (88.9)
150-300	49 (13.1)	4 (8.2)	45 (91.8)
>300	25 (6.7)	5 (20)	20 (80)
Calcium, mmol/l			
<2.1	109 (29.2)	13 (11.9)	96 (88.1)
2.1-2.37	157 (42.1)	18 (11.5)	139 (88.5)
>2.37	51 (13.7)	5 (9.8)	46 (90.2)
Phosphate, mmol/l			
<0.8	5 (1.3)	1 (20)	4 (80)
0.8-1.3	62 (16.6)	7 (11.3)	55 (88.7)
1.3-1.8	101 (27.1)	15 (14.9)	86 (85.1)
1.8-2.2	70 (18.8)	5 (7.1)	65 (92.9)
>2.2	82 (22)	8 (9.8)	74 (90.2)
Ca X PO4 product, $mmol^2/L^2$			
<3.5	127 (34)	18 (14.2)	109 (85.8)
3.5-4.5	86 (23.1)	7 (8.1)	79 (91.9)
4.5-5.5	57 (15.3)	5 (8.8)	52 (91.2)
>5.5	41 (11)	6 (14.6)	35 (85.4)

Data are presented as n (%).

Table 2 shows the detail overall cumulative survival of ESRD patients initiated on hemodialysis in Kelantan in percentage. Patients of age more than 75 years old, female gender, hemoglobin less than 10g/dl, albumin less than 30g/l, ALP more than 300 U/L had a lower survival rate at about 78.9, 85.1, 88.7, 83.7, and 70.6 respectively.

From the Table 2, there was one prognostic factor that significantly influences the mean survival of the patients and this is female gender. On the other hand, age above 75 years and albumin level below 30g/l were marginally insignificant prognostic factors for mean overall survival, as evident from its p values which barely exceed the nominal significance level of 0.05 (0.074 and 0.059 respectively).

Based on demographic characteristics, the overall survival was significantly lower in patients age 75 years and older (78.9%) than patients below the age of 75 years old with a *p*-value of 0.036. Female

Table 2: Overall survival probabilities and factors affecting first-year mortality of ESRD patients initiated on hemodialysis in Kelantan.

Factors	Overall survival					
	Cumulative survival (%)	95% CI of Cumulative survival	Deaths (n)	Censored (n)	Log-rank statistics (df)	P values
Age						
<45	95	90.3 to 99.9	4	80	6.922 (3)	0.074
45-65	90.4	86.3 to 94.6	19	174		
65-75	84.4	76.7 to 92.9	12	65		
>75	78.9	62.3 to 99.6	4	15		
Gender						
Male	93.5	90.1 to 97.0	13	186	7.116 (1)	**0.008**
Female	85.1	79.9 to 90.5	26	148		
Co-morbidity Hypertension						
Yes	93.7	90.3 to 97.2	12	178	0.221 (1)	0.638
No	91.3	80.5 to 100	2	21		
Diabetes Mellitus						
Yes	93	88.8 to 97.3	10	132	0.522 (1)	0.699
No	94.4	89.2 to 99.9	4	67		
IHD						
Yes	96.6	90.13 to 100	1	28	0.522 (1)	0.47
No	92.9	89.3 to 96.7	13	171		
Hemoglobin, g/dl						
<10	88.7	85.2 to 92.4	33	260	0.108 (2)	0.947
10-12	87.2	77.3 to 98.3	5	34		
>12	90.9	75.4 to 100	1	10		
Albumin, g/l						
<30	83.7	76.8 to 91.1	17	87	4.926 (2)	0.085
30-35	89.7	83.8 to 96.0	10	87		
>35	92.5	88.3 to 96.8	11	135		
ALP, U/l						
<150	88.9	85.2 to 92.8	29	261	2.505 (2)	0.286
150-300	91.8	84.5 to 99.8	4	49		
>300	80	65.8 to 97.3	5	25		
Calcium, mmol/l						
<2.1	88.1	82.2 to 94.4	13	96	0.134 (2)	0.935
2.1-2.37	88.5	83.4 to 93.3	19	139		
>2.37	89.8	81.7 to 98.7	5	46		
Phosphate, mmol/l						
<0.8	80	51.6 to 100	1	4	3.142 (4)	0.534
0.8-1.3	88.7	81.2 to 96.9	7	55		
1.3-1.8	85.1	78.5 to 92.4	15	86		
1.8-2.2	92.9	87.0 to 99.1	5	65		
>2.2	90.2	84.0 to 96.9	8	74		
Ca X PO4 product, $mmol^2/L^2$						
< 3.5	85.8	80.0 to 92.1	18	109	2.736 (3)	0.434
3.5-4.5	92	86.4 to 97.9	7	79		
4.5-5.5	91.4	86.4 to 98.9	5	52		
>5.5	85.4	75.2 to 96.9	6	35		

Table 3: Prognostic factors for overall survival of ESRD patients using simple Cox regression analysis.

Factors	b[a]	Crude HR (95% CI)[b]	LR statistics[c]	P value[d]
Age				
<45	-1.51	0.22 (0.06, 0.88)	4.57[e]	**0.033**[f]
45-65	-0.82	0.44 (0.15, 1.29)	2.23[e]	0.135[f]
65-75	-0.34	0.71 (0.23, 2.21)	0.34[e]	0.558[f]
>75	0	1		
Gender				
Male	0	1		
Female	0.88	2.41 (1.24, 4.68)	6.67	**0.01**
Albumin	-0.06	0.94 (0.89, 0.98)	6.84	**0.009**

[a]Regression coefficient (standard errors of regression coefficient); [b]Hazards ratio (95% confidence interval for hazards ratio); [c]Likelihood ratio statistics; [d]P value for LR statistics.

Table 4: Prognostic factors for overall survival of ESRD patients by Multiple Cox Proportional Hazard Regression Model.

Factors	B (SE)[a]	Adjusted HR (95% CI)[b]	LR statistics[c]	P value[d]
Gender				
Male	0	1		
Female	0.88 (0.34)	2.40 (1.23, 4.69)	6.51	**0.011**
Albumin, g/l	-0.07 (0.03)	0.93 (0.89, 0.98)	7.40	**0.007**

[a]Regression coefficient (standard errors of regression coefficient); [b]Hazards ratio (95% confidence interval for hazards ratio); [c]Likelihood ratio statistics; [d]P value for LR statistics.

had lower overall survival (85.1%) compared to male (93.5%) with a *p*-value of 0.009.

Based on simple Cox regression analyses (Table 3), variables that were found to be statistically significant were age, gender, and albumin level and were further analyzed in the multiple Cox regression analysis.

Forward stepwise LR selection method and backward stepwise LR selection method were implemented and resulted in the same regression model. The significant prognostic factors after adjusting for other variables in multiple Cox regression analysis were gender [b = 0.88, HR (95% CI) = 2.40 (1.23, 4.69), *P* = 0.011] and albumin [b = -0.07, HR (95% CI) = 0.93 (0.89, 0.98), *P* = 0.007]. The result of the preliminary main effect model is shown in Table 4.

The final model of the prognostic factors for mortality in ESRD patients is shown in Table 5.

Forward stepwise (LR) Cox proportional hazards regression model applied. Hazard function plot, LML plot and Schoenfeld residuals were applied to check the model assumption. Multicollinearity and interaction term were checked and not found.

The model can be interpreted as:

- Those female patients had 2.4 times higher risk of death compared to male patients, after adjusting for albumin.
- Each unit increase in albumin level was expected to decrease the risk of death by 0.94 times, after adjusting for sex.

Discussion

This study had analyzed the prognostic factors which may affect the first-year mortality of ESRD patients which was initiated on hemodialysis in all hemodialysis center in Kelantan. The results demonstrated that ESRD patient's prognosis in Kelantan was comparable to other developed countries. Significant differences in survival probabilities in few variables characteristics were identified and among them, female gender and serum albumin less than 30g/l were found to be independent after adjusting for other variables.

Table 5: Prognostic factors for overall survival of ESRD patients.

Factors	Simple Cox Proportional Hazard Regression		Multiple Cox Proportional Hazard Regression	
	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Gender				
Male	1	0.01	1	0.011
Female	2.41 (1.24, 4.68)		2.40 (1.23, 4.69)	
Albumin, g/l	0.94 (0.89, 0.98)	0.009	0.93 (0.89, 0.98)	0.007

Profile of study subjects

The mean age of patients in this study (55 years) was considerably younger to that reported by other observational survival studies in the West. Their subjects' mean age was consistently reported more than 60 years old [9-12]. This figure presumably reflects the relatively early age of ESRD in Kelantan.

Slight male to female predominance in ESRD was the known. The female percentage in all studies in the West and Singapore was 45% which is similar to this study [9-14].

Ethnic variation was not considered in this study as it was incomparable to other studies because the majority of the population in Kelantan comprises of Malaysia.

The percentage of patients with co-morbidity of diabetes mellitus and hypertension in our study at 38 and 50.9 percent respectively with hypertension predominant and this is similar observations compare to some previous studies. Wagner *et al.* (2011), Cherukuri and Bhandari (2009) reported 27.5, and 36 percent respectively. Otherwise, Chua *et al.* (2014) reported 68.3 percentage of diabetes mellitus and 92.3 percentage of hypertension with hypertension being the higher co-morbid in ESRD patients. More percentage of males had ischemic heart disease than their counterparts with the overall percentage of 7.8 percent which is lower compared to previous studies. Bradbury *et al.* (2007), Wagner *et al.* (2011), Cherukuri and Bhandari (2009) and Chua *et al.* (2014) reported 51.8, 34.6, 36 and 33.4 percent respectively. Differences in the method of retrieving the data might explain this discrepancy.

Overall survival probabilities of End Stage Renal Disease in Kelantan

The overall survival probability generated from this study showed an initial descending with gradually reducing right tail by time (Figure 1). This indicated the probability of dying was highest in the first 365 days of initiation of hemodialysis. A similar pattern of overall survival curves was also demonstrated by other studies [10-14].

All causes of death as in this study were the primary endpoint.

An issue that can complicate in survival study is the date of censor because the researchers' choice would affect the survival time [15]. For example, taking the last date of blood investigations entered in ADNAN for those patients who were not known to have died would underestimate survival. This study tried to be consistent with how

other studies had dealt with this issue. However, most survival studies did not detail out their time. Therefore, after balancing information from the results and expert opinion, the researcher takes the date of the closure of the studies as the end date for the censored populations.

Nevertheless, these study overall survival results were generally comparable with the results of other studies. The overall first-year survival in our study at 89 percent was approximately similar to studies in Singapore [11], and the US [14]. It was comparatively higher than the study in the UK [10-12].

Our population considerably comparable high survival could be probably attributed to our predominantly younger study population as compared to the Western studies. These young survivors are thought to initiate hemodialysis earlier and more compliant with treatment and their follow up. They would respond well to the treatment given.

However, in studies conducted by Lukowsky *et al.* (2007) the mortality was in the upgoing trend at 2 years and 5 years of initiation of hemodialysis whereby 5 years the mortality had increased from 36 to 74 percent. This is opposed to studies conducted by Browne *et al.* (2010) where mortality in the first year and 5 years of initiation of HD was 56 and 41 percent respectively.

Based on those findings, there were probably variations in the trend of first-year and 5-year mortality in ESRD initiated on regular HD. Hence, further local research in the future is strongly indicated to evaluate the changes in ESRD survival rate in our own population.

Survival probabilities for End-stage Renal Disease in Kelantan in specific groups

In general, the pattern of one survivorship function lying above another means, the group defined by the upper curve lived longer or had a more favorable survival experience, than the group defined by the lower curve. The survival curves pattern may provide a better description of the survival function of a given group variable. The log-rank test which was used for comparison of survivorship function in this study was based on differences in the values of observed and expected number of event calculated for each independent variable group [16]. The significant differences in the survival probabilities gave information on which group variables that potentially affected survival in ESRD patients.

Descriptively comparing of the variables' survival probabilities with other countries gave more insight on the individual variable assessed in this study. The similarity of survival probabilities of each subgroup compared to findings from other studies might confirm the importance of relevant variables. Otherwise, variables that showed differences in survival rate raised the question of its importance and need to be explained. Moreover, the survival probabilities pattern and differences provide extra information on certain important variables in our setting which have not been described widely by other researchers.

Data from this study suggested that patient above 75 years old, being female patient and serum albumin less than 30g/l have a higher mortality rate.

Similar to our result, a study by Cherukuri and Bhandari (2009), Chua *et al.* (2014), and Bradbury *et al.* (2007) showed age more than 75 years old significantly associated with a lower survival probability of ESRD patients during first-year of initiation of regular hemodialysis.

In our study, being a female is a significant factor that affects the first-year mortality. About 50 percent of the female patients in our study were between the ages of 45 to 64 years old with another 25 percent between 65 to 74 years old. This means that the majority of our female population was at premenopausal and postmenopausal age. There were many literatures which comprehensively study the gender differences in ESRD patients and found that female had higher mortality compared to male once started on hemodialysis due to many reasons such as increased leukocyte telomere length (a determinant of cell survival linked to cardiovascular disease and mortality [17]), presence of certain risk factors may be more detrimental for women than for men, and vice versa [18] such as gout [19] and hypogonadism [20].

In women, the prevalence of cardiovascular risk factors are lower compared to men [22-25] and therefore they have a longer life expectancy [21]. Similarly, the men progress to ESRD faster than women; therefore more men are initiated on dialysis compared to women [26-28]. Men also have a higher eGFR during the initiation of hemodialysis compared to women [29-31]. However, once they are started on dialysis the women population have poor survival [32-34] and this poor survival persists even after transplantation [35].

Despite there was evidence that men have worse risk profile in incident dialysis, both sexes die at an equal rate. It was observed that men who smoke had a higher prevalence of cardiovascular disease [34] and were also more likely to develop left-ventricular hypertrophy [36], cardiovascular calcification [37], and secondary hyperthyroidism with adynamic bone disease [38,39].

In women on dialysis, they had increased leukocyte telomere length (a determinant of cell survival linked to cardiovascular disease and mortality [17]), as compared to men [40]. A negative correlation between age and telomere length was reported in female but not present in the males [17]. This is in accordance with Fitzpatrick et al. 2006, showing that in the general population CRP was associated with reduced telomere length in aged males, but not in matched females.

Certain risk factors were more detrimental if present in women compares to men [18]. Such risk factors were gout [19], and diabetes mellitus [41]. These were in line with non-renal populations where the diabetic women are at a higher mortality risk than diabetic men [42-44]. Also, a previous report showed a slightly increased mortality risk in women who had type 2 diabetic ESRD patients and aged more 60 years [32]. The reason proposed were due to increased prevalence of CVD risk factors in diabetic women with disparities in medical care between sexes [42].

Another interesting area is the relation between inflammation, muscle mass and outcome [45]. There was a suggestion that the presence of inflammation provides certain protection in women compared to men [46]. Poor outcome predictors for women would be the markers of muscle strength and muscle mass [47]. Signs of muscle atrophy are more commonly seen in women [48], and genetic variations in IL-1 gene, putatively associated to increased systemic inflammation, have been associated with poor nutritional status in men, but not in women [49]. Our study was not powered to look at the possible association of high inflammatory state and nutritional state between the male and female patients for the 1st year mortality. Considering high inflammatory state predispose to mortality this should be considered in the future study.

Young uremic women usually experience premature menopause, approximately 4.5 years earlier on average than their non-uremic counterparts [20], and postmenopausal women on dialysis also have abnormally low serum estrogen levels [50]. Hypogonadism in women has been linked to sleep disorders, depression, urinary incontinence and, in the long term, to osteoporosis, impaired cognitive function and increased cardiovascular risk [20].

In a Japanese study of chronic hemodialysis patients, the authors assessed gender differences in the relationship between self-efficacy and objective compliance, finding that female patient who had higher self-efficacy were less compliant [51].

Patient's sex needed to be taken into account when making medical decisions as they were differences in responses to drug treatment which was due to physiological differences such as body weight, height, body surface area, total body water, and the amount of extracellular and intracellular water, as well as differences in pharmacokinetics or pharmacodynamics [52]. However, treatments are often universal and dosage seldom varies according to the patient's sex. There was a suggestion of overestimation of the adequacy of dialysis by kt/v in women [53]. This is due to sex limitations of the denominator of the formula (V, urea distribution volume) [54]. This explained why women with Kt/V > 1.53 had a significantly lower mortality than those with Kt/V > 1.16, an effect opposite to that seen in comparable men which were observed in HEMO study and others [55-57].

Other studies have also demonstrated that women more often receive shorter dialysis (<12h/week) than men [58] or that women are less likely to receive arteriovenous fistulas (AVF) [59,60]. Concerning the latter, some reports showed increased AVF failure in women [61,62].

In our study, the comparison between both genders was done and there were no big differences found between the mean ages, co-morbidity, baseline blood parameters. The baseline hemoglobin, albumin, calcium, phosphate, and calcium-phosphate products were comparable between both genders. These provide an opportunity for next study to include other parameters such as echocardiography findings, serum uric acid, kt/v, and dialysis access to discriminate factors that predispose female gender in Kelantan to higher mortality during first-year of initiation of hemodialysis compare to their counterparts.

Another group variable which significantly related to differences in survival probabilities is serum albumin less than 30g/l. Lukowsky *et al.* (2007), Chua *et al.* (2014), and Bradbury *et al.* (2007) shown the similar findings as our study. Hypoalbuminemia is frequently ascribed to anorexia and malnutrition. Some studies suggest a more complex etiology such as chronic inflammation and acidosis with CKD [63]. Besides that, albumin is also a negative acute-phase reactant, and low levels could signify severity of acute illnesses of acute illnesses at dialysis initiation that implies poorer prognosis.

Although informative, the unadjusted differences in survival probabilities result in the above-mentioned variables were not conclusive to accept them as predictors of ESRD mortality because they are not independent. Consideration of the confounding effect of other variables needs to be taken into consideration. Thus, after adjusting other variables in the multivariable analysis, age more than 75 years old does not independently influence the risk of first-year mortality in ESRD patients initiated on HD.

As opposed to studies by Messana *et al.* (2009), Servilla e*t al.* (2009) and Cherukuri and Bhandari (2009) where they found that low haemoglobin level, less than 10g/dl during initiation of HD is associated with high mortality during the first-year, we found that serum haemoglobin level does not significantly influence the first-year mortality rate in ESRD on HD in Kelantan even though 80 percent of ESRD patients in Kelantan had serum haemoglobin level of less than 10g/dl. Among the patients who had first-year mortality, most of them also had serum hemoglobin of less than 10g/dl. It was not statistically significant probably due to the good management of anemia with early initiation of erythropoietin and blood transfusion during dialysis. We did not put these factors in our studies due to difficulties in obtaining this information from the ADNAN system. This gives an opportunity for future studies to consider these factors.

Blood investigations such as serum ALP, calcium, and phosphate which reflect the mineral metabolism is an important risk factor for vascular calcification, cardiovascular disease and subsequently the mortality in patients with ESRD on HD does not significantly associated with mortality in our patient. This is similar to Browne *et al.* (2014), Lukowsky *et al.* (2007), and Wagner *et al.* (2011).

Raised ALP was associated with poor survival according to Kalantar *et al.* (2009) and Chua *et al.* (2014) as increased ALP was linked to vascular health. It caused vascular calcification by an increased in the hydrolysis of pyrophosphate which is a potent inhibitor of vascular calcification [64]. The ESRD patient is Kelantan mostly had ALP level of less than 150U/l and it had no significant association with the first-year mortality.

Usually, there was a high rate of coronary calcification among young hemodialysis patient. This explained mortality in patient with high calcium in ESRD as tertiary hyperparathyroidism is one of the common complications. Most of our patients have normal serum calcium of between 2.1 and 2.37 mmol/L, with only 13 percent had a calcium level of more than 2.37mmol/L. This is most probably related to the duration of diagnosis of ESRD in our patients where tertiary hyperparathyroidism had not occurred yet. This could not be confirmed with iPTH level due to a large amount of missing data.

Serum phosphate is elevated in a patient with CKD especially when GFR less than 30ml/min. High phosphate may cause development and progression of secondary hyperparathyroidism. When the product of serum calcium and phosphate are elevated this predisposes to metastatic calcification. Surprisingly, our patient had serum phosphate level within normal range 1.3 to 1.8 mmol/l. It was not significantly associated with first-year mortality in ESRD patients. This is probably because our patient was initiated with phosphate binder early and due to the younger population of our patient, they were more likely to be compliant with medications and also diet restriction that was advised. Unfortunately, we are unable to make a proper association between this as it was not included in our study.

Calcium phosphate product had a significant association with the vascular burden. High calcium phosphate product adversely affects the mortality. This association presents even before the initiation of HD [10]. In our study, the calcium phosphate product was in the normal range with most of them have a calcium phosphate product of fewer than 35mmol^2/L^2.

Conclusion

This study has provided important prognostic data and information for patients with ESRD who is going to be subjected to

hemodialysis. The overall survival probabilities of ESRD during first-year of initiation of hemodialysis in Kelantan were considerably high and comparable to other Western studies.

This study population is generally younger compared to other studies with equal gender distribution.

Three prognostic factors were found to be significant at the simple Cox regression analyses for overall survival, age, female gender, and albumin level. However, on multiple Cox proportional hazard regression, only two variables (female gender and albumin less than 30g/l) are significant prognostic factors for overall survival.

Therefore, for female patient and patient with low albumin, we need to be more careful in the initiation of hemodialysis. Primary prevention remains ultimately important to prevent ESRD. If the prognosis is to be improved, effective strategies for the identification and appropriate treatment of high-risk patients must be established.

There are several methodological limitations during the execution of the study. Ergo, further studies should be conducted in the future with the purpose of addressing the weakness encountered during the conduct of this study. Hopefully, this will lead to the obtainment of more valid estimates for each prognostic factor that influence the overall survival of ESRD patients during the first-year initiation of hemodialysis.

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