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Prognostic Factors of Renal Survival among Chronic Kidney Disease Patients in Tertiary Care Centre in Kelantan, Malaysia

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Chronic kidney disease (CKD) has the potential to evolve towards end-stage renal disease (ESRD) rather than being a functionally static process. The study aimed to identify the prognostic factors of renal survival in CKD patients. This study was a retrospective cohort study, which involved the medical record review of CKD patients between January 2005 and December 2015 in one of the tertiary referral hospitals in Malaysia. All CKD patients were included, whereas patients who were transferred out to other hospitals and had incomplete data were excluded from the study. Cox proportional hazards regression was implemented to assess the prognostic factors for renal survival among CKD patients. The significant prognostic factors that influence renal survival were smoking status (adjusted hazard ratio (HR): 2.19; 95% confidence interval (CI): 1.53, 3.13; $p<0.001$), hyperlipidaemia (adjusted HR:1.87; 95% CI: 1.34, 2.60; $p<0.001$), use of analgesics (adjusted HR: 1.87; 95% CI: 1.21, 2.8; $p=0.005$), use of functional GI disorder drugs (adjusted HR: 1.42; 95% CI: 1.07, 2.01; $p=0.016$), use of lipid lowering agents (adjusted HR: 1.41, 95% CI: 1.02, 1.97; $p=0.039$), use of corticosteroid (adjusted HR: 2.10; 95% CI: 1.25, 3.55: $p=0.005$), level of glomerular filtration rate (GFR) (adjusted HR: 0.96; 95% CI: 0.98, 0.99; $p=0.001$), level of urea (adjusted HR: 1.03; 95% CI: 1.01, 1.05: $p<0.001$) and level of creatinine (adjusted HR: 0.98; 95% CI: 0.97, 0.99; $p<0.001$). Patients who were smokers, had hyperlipidaemia, took medications, include analgesics, functional GI disorder drugs, lipid-lowering agents and corticosteroids as well as level of urea had more hazard for worse renal survival, while level of GFR and creatinine had lower hazards for worse renal survival.

Keywords: cox regression; end stage; prognostic factor; renal disease; renal survival

I. INTRODUCTION

Chronic kidney disease (CKD) is a severe health concern that impacts patients' lives, raises mortality and morbidity rates, and adds to socioeconomic issues on a global scale. Around the world, CKD affects 843.6 million individuals (Jager *et al.*, 2019). Patients with CKD are estimated to be twice the number of people with diabetes worldwide and more than twenty times the number of people affected by human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) (Jager *et al.*, 2019).

In Malaysia, the prevalence of CKD was 15.48% in 2018, with stages I and II accounting for 3.85%, stages I and II for 4.82%, stages III and IV for 6.48%, and stages IV and V for 0.25% (Saminathan *et al.*, 2020). Since the previous study indicated a prevalence of 9.07 in the year 2011, there has been an increase in CKD prevalence in Malaysia. The increasing prevalence of non-communicable diseases, as well as changes in population demographics, are the key reasons for this upward trend (Saminathan *et al.*, 2020).

In contrast to being a functionally static state, CKD has the potential to advance to end-stage renal disease (ESRD). According to the 2019 Global Kidney Health Atlas survey by

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the International Society of Nephrology, 759 per million populations worldwide were receiving ESRD treatment (Thurlow *et al*., 2021).

Significant risk factors for ESRD were age, family history, obesity, hypertension, and diabetes mellitus. Heavy metal exposure, excessive alcoholic beverage use, smoking, and analgesic drug use can all worsen kidney disease. Comorbid diseases that can result in ESRD include acute renal damage, a history of cardiovascular disease, hyperlipidaemia, metabolic syndrome, hepatitis C virus, HIV infection, and cancer.

Undoubtedly, identifying the predictive factors that contribute to and exacerbate ESRD will help to lower morbidity and death. The goal of the current investigation was to identify the prognostic factors of renal survival in CKD patients taking into account the association of some characteristics with ESRD. A well-documented study on renal survival in all stages of CKD, from diagnosis to end-stage, is also lacking in Malaysia.

II. MATERIALS AND METHODS

A. *Study Design and Population*

All CKD patients registered at Hospital Universiti Sains Malaysia (USM), Kubang Kerian, Kelantan, Malaysia between January 2005 and December 2015 were included in a retrospective cohort analysis. CKD patients with dialysis were also included in the study, but patients who were discharged to other hospitals or had missing data were excluded.

B. Sample Size

Power and Sample Size Calculation (PS) software's survival formula was used to determine the sample size. The computation revealed that, after considering in 20% of potential missing data or loss to follow-up, the necessary sample size was 270 patients. During the recruitment period, 247 CKD patients met the inclusion and exclusion criteria. Thus, 247 patients were approved for this study since the number of samples was acceptable even before accounting for 20% of the missing data. Then, simple random sampling was used.

C. Data Collection

From the patients' medical records, the researcher retrieved information on the sociodemographic, underlying disease, clinical characteristics, laboratory parameters, and treatment. Based on the CKD staging, patients were classified as either having ESRD or not. Patients with CKD who progressed to stages IV and V were classified as having ESRD.

Age, gender, race, smoking and alcohol use, comorbidities of CKD (hypertension, diabetes mellitus, hyperlipidaemia, structural renal disease, cardiovascular disease, gout, anaemia), type of medicine, and clinical traits of CKD patients were split into independent factors.

D. Statistical Analysis

The Statistical Package for Social Science (SPSS) version 27.0 (IBM Corp 2020) and STATA/SE software version 11.0 (Stata Corp 2009) were used to analyse the data. Depending on the distribution's normality, the mean with standard deviation (SD) and median with interquartile range (IQR) for continuous variables were both used. For categorical data, frequency (n) and percentage (%) were employed.

The prognostic factors for renal survival among CKD patients served as the outcome factor in a survival study. From the initial date of CKD diagnosis through the initial date of proven ESRD or usage of dialysis, renal survival was calculated. In order to increase the likelihood of detecting the patient's survival status, patients were followed up on for at least a year, from 1 January through 31 December 2016, especially for those who were enrolled at the end of the study. If the patient did not develop ESRD or did not require dialysis, the patients were regarded as censored.

The prognostic factors were discovered using both simple and multiple Cox regression. The results are shown as a hazard ratio (HR), 95% confidence interval (CI), and p-value. The cutoff for statistical significance was $p<0.05$.

E. Ethical Issue

Approval was obtained from the Human Research Ethics Committee, USM while permission to access the patient's folder was obtained from the director of the hospital. As a result of the retrospective nature of the study, patient

agreement was not necessary. The researcher provided each patient with an anonymous, confidential code numbering during the data extraction process. Since the information was entered into a password-protected computer with restricted access, it was held in tight confidence.

III. RESULTS

A. Socio-demographic Profiles of CKD Patients

Out of 247 CKD patients, 193 (78.1%) progressed to ESRD. Table 1 summarised the socio-demographic characteristics of CKD patients. The mean age of CKD patients was 53.45 years, with an SD of 8.83. Males accounted for 60.3% of the population, while Malay ethnicity was the most common (88.6%). The majority of them (70.2%) were non-smokers and non-alcohol drinkers (96.9%).

Table 1. Socio-demographics profiles of CKD patients in Hospital USM (n=247)

	Patients' Status, n (%)		
	ESRD	**Censored**	**Total**
Age (years)[a]	53.67 (8.60)	52.65 (9.64)	53.45 (8.83)
Gender			
Male	110 (57.0)	39 (72.2)	149 (60.3)
Female	83 (43.0)	15 (27.7)	98 (39.3)
Ethnicity			
Malay	172 (89.6)	46 (85.2)	218 (88.6)
Non-Malay	20 (10.4)	8 (14.8)	28 (11.4)
Smoking status			
Non-smoker	129 (73.3)	31 (59.6)	160 (70.2)
Smoker	47 (26.7)	21 (14.8)	68 (29.8)
Alcohol status			
Non-drinker	171 (96.6)	51 (98.1)	222 (96.9)
Drinker	6 (3.4)	1 (1.9)	7 (3.1)

[a]mean(SD)

Hypertension was the most common comorbid among CKD patients (90.7%), followed by diabetes mellitus (66.0%), structural renal disease (61.6%), hyperlipidaemia (55.5%), cardiovascular disease (47.0%), anaemia (40.1%), and gout (10.1%). There were 21 (8.5%) and 39 (15.8%) CKD patients who had a family history of hypertension and diabetes mellitus, respectively. Only 8.5% of CKD patients had a history of acute kidney injury, while 17.2% had a history of contrast-induced nephropathy.

The majority of CKD patients consumed vitamins (82.5%) and mineral supplements (57.9%). For treatment due to comorbid, most CKD patients took lipid-lowering agent (56.5%), followed by anti-diabetic drug (52.0%), functional gastrointestinal (GI) disorder (50.4%), cardiac therapy (49.3%), diuretic drug (47.2%), beta-blocker (40.2%), hypotensive agent (39.0%), antithrombotic agent (29.7%), analgesic (17.5%), hyperuricemia (11.8%), corticosteroid (9.9%) and anti-anaemic preparation (4.5%).

CKD patients were predominantly in the advanced stages (stage IV and V) (78.9%). The mean glomerular filtration rate (GFR) for those who had CKD was 29.37 (SD 23.67) mL/min. The mean of systolic blood pressure (SBP) for CKD patients was 145.40 (SD 29.19), whereas the mean of diastolic blood pressure (DBP) was 82.70 (SD 15.91).

B. Prognostic Factors of Renal Survival in CKD Patients

Smoker patients (adjusted HR: 2.19, 95% CI: 1.53, 3.13) and patients with hyperlipidaemia (adjusted HR: 1.87, 95% CI: 1.34, 2.60) had a higher risk of progression to ESRD.

Patients took medication of analgesics (adjusted HR: 1.87; 95% CI: 1.21, 2.88), functional GI disorder drugs (adjusted HR: 1.42; 95% CI: 1.07, 2.01), lipid-lowering agents (adjusted HR: 1.41, 95% CI: 1.02, 1.97), and corticosteroid (adjusted HR: 2.10; 95% CI: 1.25, 3.55) had a higher risk of progression to develop ESRD compared to patients without.

Every 1 mL/min increase in GFR level had a 4% lower risk of progression to ESRD (adjusted HR: 0.96; 95% CI: 0.98, 0.99). For urea, every 1 mmol/L increase in the level had a 3% higher risk of progression to ESRD (adjusted HR: 1.03; 95% CI: 1.01, 1.05). For creatinine, every 1 µmol/L increase in the level had a 2% lower risk of progression to ESRD (adjusted HR: 0.98; 95% CI: 0.97, 0.99).

Table 2. Prognostic factors of renal survival among CKD patients (n=247)

Variables	b	Adjusted HR (95% CI)	*P*-value
GFR (mL/min)	-0.01	0.96 (0.98, 0.99)	0.001
Smoking status			
Never	0	1	-
Smoker	0.78	2.19 (1.53, 3.13)	<0.001
Hyperlipidemia			
No	0	1	-
Yes	0.62	1.87 (1.34, 2.60)	<0.001
Lipid-lowering agents			
No	0	1	-
Yes	0.35	1.41 (1.02, 1.97)	0.039
Analgesics			
No	0	1	-
Yes	0.62	1.87 (1.21, 2.88)	0.005
Functional GI disorder			
No	0	1	-
Yes	0.39	1.47 (1.07, 2.01)	0.016
Corticosteroid			
No	0	1	-
Yes	0.74	2.10 (1.25, 3.55)	0.005
Urea (mmol/L)	0.03	1.03 (1.01, 1.05)	<0.001
Creatinine (µmol/L)	-0.001	0.98 (0.97, 0.99)	<0.001

IV. DISCUSSION

This study identified several important prognostic factors for renal survival in CKD patients, including smokers, hyperlipidaemia, use of analgesics, use of functional GI disorder drugs, use of lipid-lowering agents, use of corticosteroid, GFR, urea and creatinine.

The current study found that CKD patients who smoke had 2.19 times (95% CI: 1.53, 3.13) higher chance of developing ESRD than CKD patients who do not smoke. Smoking increases the likelihood of CKD progressing to ESRD, according to prior research. A study among Singaporean Chinese participants found that smoking raised the risk of ESRD by 1.29 times (95% CI: 1.02, 1.64) (Choi *et al.*, 2019).

Smoking has been linked to the development of CKD and a higher risk of ESRD (Omar *et al.*, 2020). Smoking increases blood pressure and urine albumin excretion, and it also has an impact on intrarenal hemodynamics (Choi *et al.*, 2019). Additionally, it has been recognised as an oxidative stressor that results in the production of reactive oxygen species and the overexpression of NADPH oxidase 4, which can increase glomerular damage, produce renal vasoconstriction, and cause salt retention (Geng *et al.*, 2019).

Additionally, smoking results in advanced glycation end products and insulin resistance, both of which damage kidney function (Omar *et al.*, 2020). This finding suggests that smoking accelerates the development of CKD. Additionally, it has been demonstrated that second hand smoke increases CKD development risk by more than 50% (Jhee *et al.*, 2019).

In addition, compared to patients without, people with hyperlipidaemia had 1.87 times the likelihood of their ESRD progressing (95% CI: 1.34, 2.60). A study from Osaka, Japan found that patients with comorbid hyperlipidaemia had a worse prognosis for their kidneys than those who did not (HR: 1.08; 95% CI: 0.88, 1.34) confirmed this conclusion (Akizawa *et al.*, 2016). Hyperlipidaemia worsens as CKD advances, leading to fatality in ESRD patients (Feroz *et al.*, 2020). Low high-density lipoprotein, high triglyceride, and normal or slightly lowered cholesterol-low-density lipoprotein levels are common in CKD patients (Feroz *et al.*, 2020; Visconti *et al.*, 2016). Delayed catabolism in ESRD patients is the cause of elevated triglyceride levels. The catabolic rate is anticipated to be lower in CKD patients because the enzyme gene is downregulated and lipase inhibitors are present (Mikolasevic *et al.*, 2017).

Treatments for functional GI disorders, corticosteroids, lipid-lowering medications, and analgesics were all prognostic factors for renal survival, with respective HRs of 1.87, 1.42, 2.10, and 1.41. The likelihood of acquiring ESRD was higher in those who underwent these four types of treatment than in those who did not. The results were consistent with a study in the United States where use of analgesic increased the risk of getting ESRD (HR: 1.10; 95% CI: 1.04, 1.16) (Han *et al.*, 2020).

According to a Norwegian study, using corticosteroids did not prevent the development of ESRD (Haaskjold *et al.*, 2022). However, Multiple Cox regression analysis in Chinese research discovered that corticosteroids independently protected the renal outcome (Chen *et al.*, 2020) and had a substantial impact on delaying the onset of ESRD (Qin *et al.*, 2020).

With regards to renal function tests, the current study found that CKD patients had a 4% lower chance of

developing ESRD for every increase in GFR of 1 mL/min (HR: 0.96; 95% CI: 0.98, 0.99). In CKD patients, declines in GFR are associated with the rapid progression of CKD to ESRD. This finding was in line with a study in Helsinki and Turkey where progression to ESRD was associated with lower baseline eGFR (Misra *et al.*, 2020; Altunoren *et al.*, 2019).

Besides, serum creatinine showed a significant result as a prognostic factor in renal survival among CKD patients. Every increase in 1 μmol/L of serum creatinine had 2% lesser risk to develop ESRD (HR: 0.98; 95% CI: 0.97, 0.99). A previous multivariate Cox regression study reported the same result where serum creatinine (HR: 1.02, 95% CI: 1.00, 1.05) remained an independent predictor of renal survival (Qin *et al.*, 2020). However, every 1μmol/L increase in serum creatinine had a higher risk to develop ESRD by 1.02 times. Creatinine is a metabolic byproduct of muscle activity, and its production is relatively constant. The kidneys regulate serum creatinine levels by eliminating it through urine. In kidney dysfunction, impaired filtration leads to creatinine accumulation, typically signalling disease progression. However, the inverse association observed in this study may be due to differences in baseline kidney function, muscle mass, or treatment effects. Patients with lower serum creatinine may have better preserved renal function, early intervention, or a response to nephroprotective therapies such as renin-angiotensin system inhibitors or SGLT2 inhibitors, contributing to improved renal survival.

Besides, the current study reported in CKD patients, for every 1 mmol/L increase in blood urea nitrogen is 1.03 times higher risk (95% CI: 1.01, 1.05) to develop ESRD. This was similar to the 2019 study in Taipei, Taiwan, that the overall risk of dialysis will increase by 1.03 times for every 1 mmol/L increase in urea nitrogen (95% CI: 1.02, 1.05) (Chang *et al.*, 2019). Also, a study among CKD Japanese patients reported similar findings where a higher level of blood urea nitrogen was associated with an increased risk of ESRD (HR, 1.23; 95% CI, 1.04, 1.45) (Seki *et al.*, 2019).

The present study highlighted some limitations including its study design as a retrospective study. Some of the records were not complete due to missing records. Therefore, to avoid affecting the accuracy of the data, those incomplete records were not included in the analysis.

Hospital USM is one of the nephrology centres in East Coast of West Malaysia. It would have been better if the data of CKD patients were taken from all centres in Malaysia. Since the sample size was lower compared to other survival studies, the sample size needs to be increased. Increasing the sample size will be more reliable and valuable for prognostic factors. Besides, the value of the HR of significant variables will be more accurate and can be used for better management for physicians.

V. CONCLUSION

In conclusion, patients who were smokers, had hyperlipidaemia, took medications include analgesics, functional GI disorder drugs, lipid-lowering agents and corticosteroid as well as level of urea had more hazard for worse renal survival, while levels of GFR and creatinine had lower hazards for worse renal survival. In order to slow the development of ESRD, the clinician can alter clinical care by concentrating on the important components.

VI. ACKNOWLEDGEMENT

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