RELATIVE SURVIVAL AND EXCESS HAZARD REGRESSION MODEL FOR PREDICTORS OF DEATH AMONG CHRONIC KIDNEY DISEASE STAGE 5 PATIENTS IN KELANTAN

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by

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TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SYMBOLS

β	Regression coefficient for Poisson regression analysis
R	Hazard ratio (in sample size calculation)
%	Percentage
≥	More than and equal to
≤	Less than and equal to

LIST OF ABBREVIATIONS

Alb	Albumin
CKD	Chronic Kidney Disease
DBP	Diastolic blood pressure
DKD	Diabetic kidney disease
DM	Diabetes Mellitus
eGFR	estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
HRPZII	Hospital Raja Perempuan Zainab II
JEPeM	Jawatankuasa Etika Penyelidikan Manusia
KDIGO	Kidney Disease: Improving Global Outcomes
MREC	Medical Research & Ethics Committee
RRT	Renal replacement therapy
SBP	Systolic blood pressure
USM	Universiti Sains Malaysia

LIST OF APPENDICES

KELANGSUNGAN HIDUP RELATIF DAN MODEL REGRESI LEBIHAN BAHAYA BAGI FAKTOR PROGNOSTIK KEMATIAN DALAM KALANGAN PESAKIT KEGAGALAN BUAH PINGGANG TAHAP 5 DI KELANTAN

ABSTRAK

Pengenalan: Penyakit buah pinggang kronik (CKD) tahap 5 dikaitkan dengan morbiditi dan mortaliti yang tinggi, mewakili beban yang besar kepada pesakit, pengamal penjagaan kesihatan, dan sumber perkhidmatan kesihatan. Kajian ini bertujuan untuk menganggar kadar kelangsungan hidup relatif dan mengenal pasti faktor kematian dalam kalangan pesakit CKD tahap 5 di Kelantan dari tahun 2015 hingga 2020.

Kaedah: Kajian kohort retrospektif ini dijalankan di Hospital Raja Perempuan Zainab II (HRPZII), sebuah hospital rujukan berpakar utama di Kelantan, Malaysia. Data dikumpulkan daripada rekod perubatan elektronik hospital, melibatkan pesakit yang didiagnosis dengan CKD tahap 5 antara 1 Januari 2015 hingga 31 Disember 2020, dengan tempoh tambahan pemantauan dari 1 Januari 2021 hingga 31 Disember 2022. Kriteria kelayakan untuk kajian ini termasuk pesakit dewasa berumur 18 tahun ke atas, merupakan penduduk Kelantan, dan didiagnosis dengan CKD tahap 5 dalam tempoh 1 Januari 2015 hingga 31 Disember 2020. Selepas mengaplikasi kriteria ini, seramai 515 orang pesakit telah dimasukkan ke dalam kajian ini. Anggaran kelangsungan hidup relatif dianggar menggunakan kaedah Pohar-Perme, manakala regresi Poisson berbilang pemboleh ubah pula digunakan untuk mengenal pasti faktor prognosis yang signifikan bagi nisbah lebihan bahaya (EHR) bagi kematian. Data demografi, klinikal, dan parameter makmal dikumpul dan dijalankan analisis. Jadual

hayat yang lengkap dikembangkan daripada jadual hayat ringkas yang disediakan oleh Jabatan Perangkaan Malaysia (DOSM).

Keputusan: Sebanyak 515 pesakit telah dimasukkan dalam kajian ini, dengan purata umur 58.05 tahun (sisihan piawai: 12.66) dan majoriti adalah wanita (56.1%). Penyakit kencing manis (DM) merupakan punca utama CKD, menjejaskan 76.3% pesakit. Bilangan pengidap anemia yang tinggi (95.1%), tahap albumin serum yang rendah (48.4%), dan paras fosfat yang tinggi (75.2%) turut dicatatkan. Kadar kelangsungan hidup relatif menurun dengan cepat, di mana kelangsungan hidup relatif satu tahun adalah 76% (95% selang keyakinan (CI): 72, 80), menurun kepada 45% (95% CI: 40, 50) pada tiga tahun, dan 29.6% (95% CI: 25, 36) pada lima tahun. Regresi Poisson berbilang pemboleh ubah mengenal pasti empat faktor utama: penyakit buah pinggang berpunca daripada penyakit kencing manis (DKD) meningkatkan risiko kematian berlebihan sebanyak 77% (EHR = 1.77, 95% CI: 1.27, 2.46, $p < 0.001$), manakala pesakit yang menerima rawatan konservatif mengalami risiko kematian tertinggi dalam tempoh enam bulan pertama (EHR = 13.56, 95% CI: 6.62, 27.76, $p < 0.001$), dengan penurunan secara beransur-ansur dari semasa ke semasa. Albumin serum yang rendah meningkatkan risiko kematian sebanyak sekali ganda (EHR = 1.99, 95% CI: 1.54, 2.59, $p < 0.001$), dan paras fosfat tinggi meningkatkan risiko kematian sebanyak 66% (EHR = 1.66, 95% CI: 1.21, 2.27, $p = 0.003$).

Kesimpulan: Kelangsungan hidup relatif dalam kalangan pesakit CKD tahap 5 di Kelantan adalah rendah dengan penurunan ketara dalam dua tahun pertama selepas diagnosis. Faktor yang signifikan bagi kematian adalah DKD, rawatan konservatif, paras albumin serum yang rendah, dan tahap fosfat yang tinggi. Pengaruh masa yang memberi kesan terhadap rawatan konservatif menekankan kepentingan pengurusan awal dan agresif. Mengoptimumkan penjagaan bagi kumpulan berisiko tinggi

terutamanya mereka yang menerima rawatan konservatif, serta menangani faktor risiko yang boleh diubah seperti tahap albumin dan fosfat, adalah penting untuk meningkatkan kelangsungan hidup populasi ini.

Kata kunci: penyakit buah pinggang kronik tahap 5, kadar kelangsungan hidup relatif, model regresi lebihan bahaya, faktor ramalan kematian.

RELATIVE SURVIVAL AND EXCESS HAZARD REGRESSION MODEL FOR PREDICTORS OF DEATH AMONG CHRONIC KIDNEY DISEASE STAGE 5 PATIENTS IN KELANTAN

ABSTRACT

Introduction: Chronic kidney disease (CKD) stage 5 is associated with significant morbidity and mortality, representing a substantial burden on patients, healthcare providers, and resources. This study aimed to estimate the relative survival rates and identify predictors of death among CKD stage 5 patients in Kelantan from 2015 to 2020.

Methods: This retrospective cohort study was conducted at Hospital Raja Perempuan Zainab II (HRPZII), a major tertiary referral centre in Kelantan, Malaysia. Data were collected from the hospital's electronic medical records, covering patients diagnosed with CKD stage 5 between 1st January 2015 and 31st December 2020, with an additional follow-up period extending from 1st January 2021 to 31st December 2022. The eligibility criteria for this study included adult patients aged 18 years and above who were Kelantan residents and diagnosed with CKD stage 5 between 1st January 2015 and 31st December 2020. After applying these criteria, a total of 515 patients were included in the final analysis. Relative survival was calculated using the Pohar-Perme method, and multivariable Poisson regression was performed to identify significant prognostic factors of excess hazard ratio (EHR) of death. Data on demographic, clinical, and laboratory parameters were collected and analysed. A complete life table for this study was derived by expanding the abridged life table provided by the Department of Statistics Malaysia (DOSM).

A total of 515 patients were included in the study, with a mean age of 58.05 years (SD: 12.66) and a female predominance (56.1%). Diabetes mellitus (DM) was the leading cause of CKD, affecting 76.3% of patients. High prevalence rates of anaemia (95.1%), low serum albumin (48.4%), and elevated phosphate levels (75.2%) were observed. Relative survival declined rapidly, with one-year survival at 76% (95% confidence interval CI: 72, 80), dropping to 45% (95% CI: 40, 50) at three years, and 29.6% (95% CI: 25, 36) at five years. Multivariable Poisson regression identified four significant predictors: diabetic kidney disease (DKD) increased excess mortality risk by 77% (EHR = 1.77, 95% CI: 1.27, 2.46, $p < 0.001$), while patients on conservative treatment had the highest excess hazard in the first six months (EHR = 13.56, 95% CI: 6.62, 27.76, $p < 0.001$), with a gradual decline over time. Low serum albumin doubled mortality risk (EHR = 1.99, 95% CI: 1.54, 2.59, $p < 0.001$), and elevated phosphate levels increased the risk of death by 66% (EHR = 1.66, 95% CI: 1.21, 2.27, $p = 0.003$).

Conclusion: Relative survival among CKD stage 5 patients in Kelantan is low, with a marked decline during the first two years post-diagnosis. Significant predictors of mortality include DKD, conservative treatment, low serum albumin, and high phosphate levels. The time-dependent effect of conservative treatment underscores the importance of early and aggressive management. Optimizing care for high-risk groups, particularly those undergoing conservative treatment, and addressing modifiable risk factors such as albumin and phosphate levels, is critical to improving survival outcomes in this population.

Keywords: CKD stage 5, relative survival, excess hazard regression model, predictors of death

CHAPTER 1

INTRODUCTION

1.1 Background

Chronic kidney disease (CKD) is a significant global health concern, with a global prevalence of 9.1% in 2017, making it the 12th leading cause of mortality across the globe (Bikbov *et al.*, 2020). From 1990 to 2016, the worldwide burden of CKD rose by 87%, highlighting its escalating influence on healthcare systems (Xie *et al.*, 2018).

In Asia, home to more than 4.5 billion individuals, the prevalence of CKD differs significantly, spanning from 7% in South Korea to 34% in Singapore. Around 434.3 million adults in Asia suffer from CKD, with 65.6 million experiencing advanced stages of the illness (cited in Liyanage et al., 2022).

Based on a systematic review and meta-analysis of studies published from 2004 up to November 2021, the global prevalence of CKD stages 3–5 is estimated at 10.6%. In Malaysia (9.0%), Thailand (12.4%), and India (11.7%), the CKD prevalences were relatively close to this global rate. However, certain countries in the region exhibit significantly higher CKD prevalence, with Bangladesh at 19.8%, Sri Lanka at 17.6%, and the Philippines at 35.9% (Suriyong *et al.*, 2022).

Malaysia, a nation in Southeast Asia with a population of 33.4 million, has experienced a concerning increase in CKD prevalence, climbing from 9.07% in 2011 to 15.48% in 2018 (Hooi et al., 2013; Saminathan et al., 2020).

The impact of CKD in Malaysia is additionally shown by the rising count of patients needing dialysis. The number of dialysis patients in Malaysia increased from 29,443 in 2012 to 49,770 in 2021, which corresponds to 1,528 per million individuals.

In 2021, Kelantan had 1,921 dialysis patients, an increase from 1,595 in 2017 (Hooi LS & Ong LM (Eds), 2023). These patterns suggest a considerable and increasing burden of CKD in Malaysia, including in Kelantan.

Between 2010 and 2016, Malaysia's expenditure on end-stage renal disease (ESRD) treatment nearly doubled, increasing from MYR 572 million (USD 405 million) to MYR 1.12 billion (USD 785 million) a 94% rise in just seven years. The share of ESRD treatment in Malaysia's total healthcare budget also increased, rising from 2.95% in 2010 to 4.2% in 2016, reflecting a financial strain on the healthcare system (Ismail *et al.*, 2019).

CKD greatly affects survival results. A Canadian cohort study discovered that CKD survival rates at one year were similar to those for nonmetastatic cancer; however, by five years, CKD patients faced a 23% greater risk of death compared to individuals with nonmetastatic cancer (Tonelli *et al.*, 2022) In a similar vein, Italian research indicated a five-year relative survival rate of 55.6% for CKD patients, which is on par with survival rates for colon and ovarian cancer in Malaysia (Nordio et al., 2012; Nureylia Amir et al, 2018). These results highlight the significance of recognizing mortality predictors and enhancing care approaches for CKD patients to reduce disease impact.

1.2 Problem Statement

Conventional cause-specific survival analysis, often employed to assess survival outcomes, relies on precise and dependable cause-of-death information. In instances of CKD and end-stage renal disease (ESRD), the main cause of death is frequently misidentified, as CKD is usually viewed as a contributing factor to various other ailments like cardiovascular diseases or infections (Seyedghasemi *et al.*, 2020). This

incorrect classification creates bias in survival estimates, reducing the dependability of cause-specific survival techniques (Schaffar *et al.*, 2017). Kelantan is not exempt from the challenges of cause-specific survival assessment, as similar difficulties exist in other regions.

Variations in life expectancy and demographic composition can complicate survival estimates, rendering cross-population comparisons unreliable (Pohar & Stare, 2007). Although Kelantan has a significant burden of CKD, the Malaysian Dialysis and Transplant Registry (MDTR) did not include region-specific evaluations of survival rates and prognostic factors. This lack of understanding obstructs attempts to create customized interventions and public health initiatives for the Kelantan community.

To overcome these limitations, different approaches to survival analysis are required. The absence of localized survival data and the constraints of current methodologies highlight the necessity for a comprehensive approach to assess CKD survival and pinpoint mortality predictors unique to Kelantan.

1.3 Study rationale

The rising prevalence and mortality rates associated with CKD in Malaysia, particularly in Kelantan, highlight the need for detailed survival analyses to guide clinical care and public health interventions. Accurate identification of predictors of mortality is critical for developing strategies to reduce the disease burden and improve patient outcomes.

Relative survival analysis offers a robust alternative to traditional cause-specific methods. By comparing observed survival rates of CKD patients with expected survival rates in the general population, matched by age, sex, and calendar year, this method accounts for background mortality without requiring cause-of-death data. Relative

survival provides a more reliable estimate of disease-specific survival and is particularly advantageous in regions where mortality data are incomplete or prone to misclassification.

This study aims to investigate the relative survival and excess hazard ratios for CKD stage 5 patients in Kelantan, incorporating demographic, clinical, and laboratory parameters. By addressing critical gaps in the literature, the findings will provide insights into the factors influencing mortality and survival trends among CKD patients in this region.

The results of this study are expected to have significant implications for public health and clinical practice. They will serve as a foundation for developing region-specific interventions, optimizing resource allocation, and reducing health disparities in Kelantan. Moreover, these findings can inform policymakers and healthcare providers in designing strategies to improve CKD management and survival outcomes.

1.4 Research Questions

1. What are the 1-year, 3-year, and 5-year relative survival rates of CKD stage 5 patients in Kelantan?
2. What are the predictors of excess hazard among CKD stage 5 patients in Kelantan?

1.5 Research Objectives

1.5.1 General objective

To examine the relative survival rates and predictors of excess hazard for CKD stage 5 patients in Kelantan from 2015 to 2020.

1.5.2 Specific objectives

1. To estimate the 1-year, 3-year, and 5-year relative survival rates of CKD stage 5 patients in Kelantan from 2015-2020.
2. To identify the predictors of excess hazard for CKD stage 5 patients in Kelantan from 2015-2020.

1.6 Research hypothesis

No hypothesis is applicable for objective 1.

For objective 2, the predictors of excess hazard for CKD stage 5 patients in Kelantan from 2015 to 2020 include older age, male gender, diabetic kidney disease (DKD) and conservative dialysis modality.

CHAPTER 2

LITERATURE REVIEW

2.1 Search strategy

To ensure a thorough review of the literature, appropriate keywords were recognized according to the study population and outcomes of interest. Related terms and synonymous phrases within the same idea were merged using the Boolean operator "OR," whereas different concepts (population and outcomes) were connected using the Boolean operator "AND". Enhanced search features in PubMed and Scopus were used, concentrating on keywords found in the titles and abstracts of research articles.

A more inclusive term like "survival" was first employed to encompass a variety of studies. Nonetheless, additional precise terms such as "relative survival," "excess mortality," and "net survival" were subsequently utilized to enhance the search. This method guaranteed both wide-ranging and in-depth identification of pertinent articles. The obtained results were loaded into the Mendeley citation manager for sorting and