Survival analysis of chronic dialysis patients

by

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Author's declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including

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Abstract

Background: The number of dialysis patients is steadily rising in Canada because of demographic changes as well as an increased prevalence of associated risk factors such as hypertension, diabetes, and aging (Clark & Khan, 2010). Therefore, survival analysis of dialysis patients and the investigation of factors associated with survival outcome is crucial. This study aimed to estimate the survival rate of dialysis patients in Grand River Hospital (GRH), compare the survival outcome of Peritoneal Dialysis (PD) and Hemodialysis (HD) patients and assess the factors affecting survival outcome.

Methods: This retrospective study was based on the data on incident chronic dialysis patients (>30 days of dialysis) who initiated dialysis from January 2012 to September 2017. Acute dialysis patients and those who initiated dialysis before the start of the study were excluded. Kaplan-Meier (KM) survival curves were generated to estimate the overall survival of the cohort as well as by different age categories, gender and, type of modality. The Cox Proportional Hazard (PH) model was used to identify variables significantly associated with survival outcome.

Results: A total of 723 incident chronic dialysis with the average age of 64.86 years contributed to this analysis. The median survival time in this population was 39.8 months. Estimated 1-, 3- and 5- year survival rates were, 0.8, 0.54 and 0.34, respectively. Using the log-rank test, there was no statistical differences in survival outcome between patients undergoing HD and PD in this study (p=0.464). Backward elimination procedure with the two cut-offs (p>0.1 and p>0.2) resulted in two models in which hypertension was found to be significant in both (model A: adjusted HR = 0.62, p=0.013; model B: adjusted HR = 0.65, p=0.023).

Conclusion: This research showed comparable survival rates for incident chronic dialysis patients receiving care in GRH, similar survival experience of HD and PD patients and protective impact of hypertension on survival outcome. Long-term survival outcome results were similar between both groups; however, PD patients had an improved survival outcome during the first 18 months of the study.

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Foremost, I would like to thank my parents, who encourage me accomplish my goals and dreams. My expression of thanks does not suffice for all they have done to me. To my wonderful husband Matin, without whom nothing is possible for me.

Dedication

My loving parents, My better half, Matin, My siblings

And

The memory of my beloved grandmother (Madar)

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List of Abbreviations

ACR	Albumin to Creatinine Ratio
BMI	Body Mass Index
CAD	Coronary Artery Disease
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCPD	Continuous Cycling Peritoneal Dialysis
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CORR	Canadian Organ Replacement Register
CVA	Cerebrovascular Accident
DBP	Diastolic Blood Pressure
DOPPS	Dialysis Outcomes and Practice Patterns Study
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
GRH	Grand River Hospital
GOF	Goodness of Fit
HD	Hemodialysis
HF	Hemofiltration
HR	Hazard Ratio
HTN	Hypertension
IHD	Ischemic Heart Disease
NKF	National Kidney Foundation
OR	Odds Ratio
ORN	Ontario Renal Network
PD	Peritoneal Dialysis
PVD	Peripheral Vascular Disease
RRT	Renal Replacement Therapy
SBP	Systolic Blood Pressure
USRDS	United States Renal Data System

Chapter 1: Introduction

Chronic Kidney Disease (CKD) refers to the progressive loss of renal function (i.e., "kidneys have not working properly to remove wastes and excess fluid from the body for at least three months"[1]). Among various medical problems, CKD is one the most serious, and its complications affect patients' lives in many ways, such as decrease of their quality of life and loss of work ability. The prevalence of CKD is rising at an alarming rate worldwide, and the National Kidney Foundation (NKF) reports that about one out of every 10 people suffers from it[2]. In Canada, the number of patients receiving treatment for kidney failure has tripled in the last two decades[2].

In the last stage of CKD, which is known as End-Stage Renal Disease (ESRD), the kidneys reach below 15 percent of their functionality (Clark & Khan, 2010). An ESRD diagnosis means that the kidneys have failed and are not working well enough to meet the daily needs of the patient's body without any replacement. Dialysis and kidney transplantation are renal replacement therapies that provide permanent treatment and help patients in this stage survive (Clark & Khan, 2012). The Kidney Foundation of Canada has reported that out of 36,251 patients with kidney failure, 58.5% are undergoing dialysis and 41.5% have a functioning

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[1] Ontario Renal Network, kidney disease, retrieved at:
http://www.renalnetwork.on.ca/info_for_patients/kidney_disease/ - .W1Tq760ZP-Y
[2,2,3] Kidney Foundation of Canada, Facing the Facts, 2017, retrieved at:
https://kidney.ca/file/kidney.ca_nat/Facing-the-Facts-Kidney-Disease-2017.pdf

transplant[3]. Kidney transplantation is the optimal treatment option in ESRD population with regards to quality of life and survival potential. However, due to the shortage of available organs, dialysis is the main care mode for ESRD patients (Valderrábano, Jofre & López-Gómez, 2001). Hemodialysis (HD) and Peritoneal Dialysis (PD) are the most commonly used types of dialysis. Survival comparison of these two therapies has been investigated in several studies but survival advantage of each modality over the other is still inconclusive (Sood et al., 2012).

In the past half-century, the widespread use of dialysis among the kidney-failure population can be considered as a remarkable achievement. Nevertheless, in spite of significant improvements in the availability of renal replacement therapies and a reduced mortality rate among ESRD patients, the mortality rate has still remained high compared with the rate in the general population (Arogundade, Sanusi, Hassan & Akinsola, 2011). The high rate of mortality among dialysis patients after initiation of the therapy can be attributed to many factors. Demographic factors, comorbidities, blood markers such as albumin and hemoglobin, and type of modality can contribute to survival (Collins, 2012). Additionally, receiving different levels of care can also affect survival, which leads to different survival rates in many countries (Wen et al., 2008; Yang & Hwang, 2008).

Our present knowledge of the reasons leading to increased mortality among dialysis patients is still incomplete. Moreover, current understanding regarding the superiority of HD and PD is not sufficient. The use of survival analysis enables important interpretation to be made in terms of impact of various factors on survival outcome as well as comparing survival rate of patients undergoing different modalities. The knowledge gained could be used to provide recommendations to personalized care plan for patients. The overall aim of this study was to

address the aforementioned knowledge gaps, to better understand the mortality determinants and survival comparison of PD and HD patients in GRH.

This thesis will be divided into six chapters. The present chapter briefly addresses the problem and general aim of the study. In the second chapter, an overview of the CKD, ESRD, dialysis and their corresponding prevalence all around the world and in Canada is reviewed. A discussion on the factors associated with the survival as well as survival analysis description is also presented in chapter two. Subsequently, in chapter three study rationale and research questions will be provided. The fourth chapter, the methodology and design of the current study, including a description of the variables, the outcome, and statistical methods will be described. Next chapter presents the results of this study, including Kaplan-Meier survival curves as well as obtained Cox regression results. In the last chapter, a discussion of the results in addition to the strengths, limitations, future direction and conclusion of this study will be provided.

Chapter 2: Literature Review

2.1. Chronic Kidney Disease

Chronic Kidney Disease (CKD) refers to a serious illness condition occurring progressively with significant health consequences. Cardio-vascular disease, hypertension and obesity consequences are among the most common causes of renal failure (Collins, 2012). Clinically, there are five stages for CKD defined based on measuring the Glomerular Filtration Rate (GFR). According to the National Kidney Foundation (NKF), End-Stage Renal Disease (ESRD) refers to the last stage of CKD in which the level of GFR is less than 15 ml/min/173m^2 [1].

In this stage, the kidneys fail to work at a level required for daily life. In fact, the gradual loss of kidney function reaches an advanced stage in which the metabolic needs of the patient's body cannot be adequately met. ESRD patients who do not have the chance to receive Renal Replacement Therapy (RRT) are prone to death due to significant metabolic dysfunction and electrolyte imbalance caused by progressive deterioration in their renal function.

Under this condition, patients require RRT which provides an artificial function of their kidney, extend life and alleviate the symptoms. RRT is considered as a life-saving intervention consist of three primary techniques, including Peritoneal Dialysis (PD), Hemodialysis (HD) and transplantation (Abecassis et al., 2008). Among these different

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[1] National kidney foundation (NKF), 2017, retrieved at: https://www.kidney.org/atoz/content/gfr

therapies, transplantation is the most preferred therapy for patients. However, due to shortage of kidney donors, majority of ESRD patients need to initiate dialysis (Abecassis et al., 2008; Sayin, Colak, Tutal & Sezer, 2013). Of note, dialysis only performs the filtering function of the kidney, which is removing metabolic waste products and balancing electrolytes. In fact, production of hormones is not performed by dialysis (Abecassis et al., 2008).

2.2.   Dialysis

Dialysis is a method of RRT, defined as the process of bidirectional flow of molecules across a semipermeable membrane. This procedure occurs in and out of the blood, across a semipermeable membrane. If molecule exchange happens outside of the body through an artificial membrane, the process is called HD or Hemofiltration (HF) (Daugirdas & Blake, 2012). If this process takes place across the peritoneal membrane, the process is named PD (Ahmad, 2009).

2.2.1. Hemodialysis

HD modality involves the extracorporeal removal of waste products (e.g., creatinine and urea). This type of modality can be categorized based on the location as in-center HD and home HD (Daugirdas & Blake, 2012). Moreover, it can be also categorized as conventional, daily, short daily, and nocturnal. Regular HD is most often conducted in a hospital setting and is offered 3 times weekly for 3-5 hours for each session. Out-patient HD can be self-initiated or managed jointly with nurses and technicians or a trained helper, usually a family member. A nephrologist decides on dialysis parameters, including session length, session frequency, blood and dialysis solution flow rates and dialyzer size. Main disadvantages of this modality are

limited independence, restricted in fluid intake, complicated procedure, and expensive settings (Daugirdas & Blake, 2012).

Moreover, HD procedure involves diffusion of solutes across a semipermeable membrane as well as fluid removal or ultrafiltration in which water and some dissolved solutes are moved across the membrane. Primarily there are two main methods for accessing blood for hemodialysis: Arteriovenous (AV) fistulas or grafts and catheter. In an AV fistula access type, an anastomosis is created between the artery and a native vein in which the blood flows directly from artery to the vein. However, in graft, the distance between the feeding artery and vein is bridged by a tube (i.e., created from a prosthetic material) (Daugirdas & Blake, 2012; Ahmad, 2009).
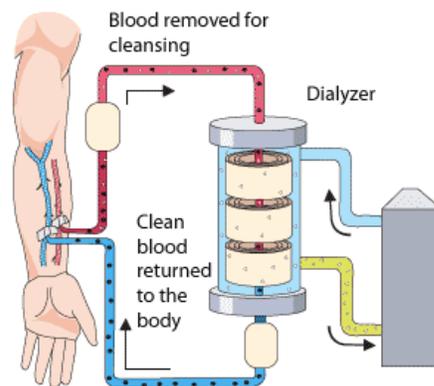
Figure 1. Schematic of the Hemodialysis (HD) procedure. From "MediResource Inc", 2018,
https://medbroadcast.com/procedure/getprocedure/hemodialysis?_ga=2.118604745.1125548109.153057
0499-774011722.1530570499

2.2.2. Peritoneal dialysis

PD provides a home-based therapy with a simple equipment setup. In this type of therapy, the flow of solutes and water circulates across a membrane that separates two fluid-containing compartments. One compartment holds blood from the peritoneal capillaries (in renal failure it contains waste products such as the excess urea, creatinine, and potassium) and the other holds dialysis solution in the peritoneal cavity (it contains sodium, chloride and lactate). During the process of PD, as with the other methods, three transport processes occur simultaneously: diffusion, ultrafiltration, and absorption.

PD is recommended more often for patients with difficult vascular access, such as infants or young children and patients with severe cardiovascular disease. This modality is less expensive (particularly in developing countries), more convenient and simpler compared to HD technique because of its home-based setting (Ahmad, 2009). There are two main types of PD: Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD)/ Continuous Cycling Peritoneal Dialysis (CCPD). In the CAPD procedure, solution changes should be performed by a patient four or five times per day; whereas these exchanges are carried out automatically in APD during the night when a patient is connected to the cycling machine (Daugirdas & Blake, 2012).
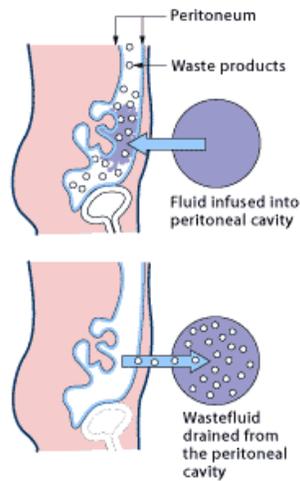
Figure 2. Schematic of the Peritoneal Dialysis (PD) procedure. From "MediResource Inc", 2018,
https://bodyandhealth.canada.com/channel/kidney-health/kidney-disease-management/peritoneal-dialysis

2.3.   ESRD and dialysis trend in Canada

ESRD patients experience a broad range of distressing symptoms such as poor quality of

life, increased risk of mortality and cardiovascular diseases (Tonelli et al., 2006). In spite of

epidemiological advances to reduce the prevalence of kidney disease globally, the prevalence

of ESRD still remains high. Kidney Foundation of Canada in 2017 has reported that the

number of Canadian suffering from ESRD has increased 36% since 2006[1]. In 2015, Canadian

Institute for Health Information (CIHI) reported that 35,281 Canadians (excluding Quebec)

were living with ESRD[2]. Out of this number 58.5% are receiving dialysis and the remaining

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[1] Kidney Foundation of Canada, Facing the Facts, 2017, retrieved at:
https://kidney.ca/file/kidney.ca_nat/Facing-the-Facts-Kidney-Disease-2017.pdf

[2] Annual Statistics on Organ Replacement in Canada: Dialysis, Transplantation and Donation, 2006 to 2015,
January 2017, retrieved at: https://www.cihi.ca/sites/default/files/document/corr-snapshot-en-webaccessible.pdf

have a functioning transplant. Moreover, patients above 65 years old were 47% of the whole number of Canadian ESRD patients[1].

2.4. ESRD and dialysis trend in Ontario and GRH

Ontario Renal Network (ORN) survey examined the trend in 2016 and presented the data as the "The Ontario 2016 CKD System Atlas". The data reported the information on CKD and ESRD patients in 26 regional CKD programs as well as the corresponding multidisciplinary clinics in Ontario from 2010 to 2015. An increasing trend has been reported in the number of incident patients with advanced CKD since 2013. The prevalence of this group of patients increased from 5335 in 2013 to 6396 in 2015 in Ontario. It is worthwhile to mention that the increase in patients count over time was higher among elderly patients (particularly over 65 years old)[2].

According to 2016 CKD System Atlas, since 2010, the provincial rate of increase in the incident number of patients initiating chronic dialysis is 3.3% annually. This number was 3069 in 2015. Out of 6396 patients newly registered in Ontario with advanced CKD, 337 new dialysis patients were registered at GRH in Waterloo region in 2015. In the duration from January 1, 2015 to December 31, 2015, 3069 patients started chronic dialysis in Ontario and GRH represents approximately 5% of the whole[1]. Different growth rate was observed across different

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[1] Kidney foundation of Canada (2017), Facing the facts about kidney disease. Retrieved at :
https://kidney.ca/file/kidney.ca_nat/Facing-the-Facts-Kidney-Disease-2017.pdf

[2] Ontario Renal Network. Ontario 2016 CKD System Atlas: Trends in Kidney Disease and Care. Toronto: Ontario Renal Network, CCO; 2016, retrieved at:
http://www.renalnetwork.on.ca/common/pages/UserFile.aspx?fileId=362165

age categories in Ontario. For example, the category of 65-74 years old patients had the highest growth rate. The number of patients initiated dialysis in 2015 was around 700 in Ontario[1].

2.5.   Distribution of modalities in Canada and Ontario

Based on the latest reports from CIHI in 2015 the number of Canadian patients who started incident chronic dialysis therapy in terms of modality were reported as follows: 76.6% institutional HD (n=4004), 0.7% home-HD (n=36), 12.6% CAPD (n=632) and 7.3% APD (n=368)[1]. According to the ORN recent report in 2016, 78.8% (n=2393) of ESRD patients were initially started the therapy with in facility-based HD and 20.7 % (n=644) with PD. The number of incident home HD patients were only 0.5% (n=15)[2].

2.6.   Survival analysis

Survival analysis refers to a popular data analysis for specific types of epidemiologic data and analytic problems. Survival analysis is defined as "a collection of statistical procedures for data analysis for which the outcome variable of interest is time until an event occurs." (Kleinbaum & Klein, 2006, p.4). There are two common concepts in the context of survival analysis, time and events. Time is measured in years, months, weeks

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[1] Annual Statistics on Organ Replacement in Canada: Dialysis, Transplantation and Donation, 2006 to 2015, January 2017, retrieved at:
 https://www.cihi.ca/sites/default/files/document/corr-snapshot-en-webaccessible.pdf
[2] Ontario Renal Network. Ontario 2016 CKD System Atlas: Trends in Kidney Disease and Care. Toronto: Ontario Renal Network, CCO; 2016, retrieved at:
http://www.renalnetwork.on.ca/common/pages/UserFile.aspx?fileId=362165

or days from the beginning of the induvial entry to the study until to the occurrence of the event of interest, such as death, disease occurrence, recovery or any other designated experience that may happen to an individual. In the context of survival analysis, "survival time" refers to the time that an individual survived over the study follow-up time period (Kleinbaum & Klein, 2006).

2.6.1. Survival analysis goals

The main purposes of survival analysis are to estimate, interpret and compare the main quantities, including survival and (or) hazard functions and also to estimate the impact of various covariates on survival time. The objectives in a survival analysis may include estimation of one or more of these statistics in specified covariate profiles and quantifying the influence of explanatory variables (e.g., treatments, demographics) on survival. These goals can be achieved through modeling how x (i.e. explanatory variables) impacts T (i.e., survival time) directly or indirectly (George, Seals & Aban, 2014).

2.6.2. Censored data

Censoring is one of the most important analytical problems for survival analysis in the design of clinical trials. It occurs when information on the times to events of interest is not available for all the included individuals in a cohort (Singh & Mukhopadhyay, 2011). An important fact about censored data is that this type of analytical problem is not considered as missing values. In other words, statistical survival analysis is able to include this type of data in building the model.

There are two types of censoring: right and left. In the context of health studies, when a patient does not experience the event of interest or outcome (i.e., lost to follow-up or experiences censoring events) during the study period, right censoring has occurred (Singh & Mukhopadhyay, 2011). Right-censored data are more common in the context of health care compared to left-censored observation (Prinja, Gupta & Verma, 2010). Left censoring refers to a condition in which the patient has been exposed to the disease before entering to a study (i.e. the exact time of exposure is not clear). In other words, the survival time is incomplete on the left-side of follow-up duration. In this study, there was no left censoring.

Figure 3 depicts the study time for eight patients in a clinical trial in which entry to the study shown is with a "●". Patients 1, 4, 5 and 8 die (D) during the study period, while patients 2 and 7 are lost to follow-up (L), and only patients 3 and 6 are still alive at the end of the study. The corresponding survival time for the individuals is calculated from entry to the study until the death of patients (D). This period can be calculated for patients 1, 4, 5 and 8. The survival times of patients 2, 3, 6 and 7 are right-censored (Collett, 2015).
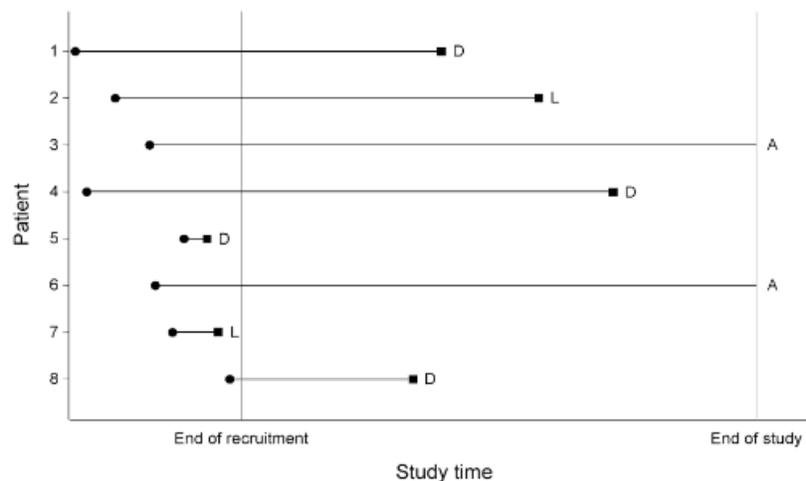
Figure 3. study time for eight patients in a survival study

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When the probability of any patient in the cohort being censored in the cohort at time t does not depend on the patient's survival outcome at time t, non-informative censoring happens (Kleinbaum & Klein, 2006).

2.6.3. Survival rate estimation

The purpose of survival rate estimation for various medical problems is to identify the average prognosis in a specific population. Consequently, the obtained survival rate in the region concerned provides an index of the effectiveness of different treatments and medical care (Parkin & Hakulinen, 1991). Survival rate can be defined as "the percentage of people in a study or treatment group who are still alive for a certain period of time after they are diagnosed with or have started treatment for a disease, such as cancer."[1] In the survival analysis context, an initial analysis would typically employ nonparametric methods to estimate the survival function and summary statistics such as survival rates, and a comparison across several groups or sub-populations (Gardiner, 2010). The widely used analytical method to estimate survival rates for population-based data is Kaplan-Meier estimator which will be discussed in Methods chapter (4.7.2).

2.7. Survival rate in dialysis patients

In the medical research context, survival analysis is generally considered as one of the most clinically relevant statistics to estimate the patients' prognosis, chance of survival or recovery,

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[1] NCI dictionary of Cancer Terms, retrieved at: http://www.cancer.gov/

and to identify the most optimized treatment plan. In public health research, survival statistics are represented by survival rates as an important indicator of health status of a specific population. Due to multiple health concerns affecting life expectancy of dialysis patients, nephrologists' efforts have been directed towards improving this rate. The last years, have seen some remarkable improvements in the field of dialysis leading to increased quality of life and facilitated dialysis procedure. Despite some evidence showing decrease in overall mortality rate over the past two decades, the survival rate and life expectancy did not improve significantly among dialysis patients (Arogundade et al., 2011).

The Canadian dialysis population experienced gradual improvement in long-term survival rates for all modalities. Reports on data from the Canadian Organ Replacement Register (CORR) demonstrated that the 5-year survival rate increased from 0.38 in 2006 to 0.43 in 2010 among hemodialysis patients[1]. Likewise, the same trend was observed for the 3-year survival rate.

Another study conducted in Korea in 2015 reviewed over 32,000 incident dialysis patients, to explore whether the survival rate improved from 2005 to 2008. Kaplan-Meier curves demonstrated statistically significantly different survival rate in terms of dialysis initiation year (p=0.005), particularly among PD patients compared to group HD (p<0.001) (Ryu et al., 2015). The 1-, 2-, 3-, and 4-year survival rate improved from 87.6, 78.2, 70.4, 64.4 in 2005 to 88.6, 80.1, 73.0, 66.8 in 2008, respectively. The significant differences in survival rates persist after multivariate analysis which revealed lower mortality risk of patients initiating any type of dialysis including PD or HD in 2005 compared to 2008. In the Cox model, age (per 1-year

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[1] Canadian Organ Replacement Register (CORR) at the Canadian Institute for Health Information (CIHI), 2016, retrieved at: https://www.cihi.ca/en/canadian-organ-replacement-register-2016

increase, HR 1.05, p<0.001) female gender (vs. male, HR 0.85, 95% CI, p<0.001) grade 5 or higher for Charlson Comorbidity index (CCI) (vs. grade 0, HR 2.67, CI 95%, p<0.001), and Medical Aid (vs. National Health Insurance, HR 1.71, 95% CI, p<0.001) were significant independent predictors of mortality. Of note, dialysis modality did not have any statistically significant impact on survival (HD vs PD, HR=0.91, p=0.052). Subgroup analysis of the cohort showed a higher survival rate of non-diabetic patients younger than 65 years old who received PD in 2008 relative to the counterparts undergoing HD. Furthermore, this study found no statistically significant differences in mortality rate among patients younger than 55 years old (Ryu et al., 2015).

Recently, in Iran a retrospective study by Shabankhani et al., (2016) analyzed the survival rate of 500 hemodialysis patients in three hospitals and also evaluated the variables influencing survival. During a 6-year follow-up the impact of gender, age, education, occupational status, smoking status, age at diagnosis, primary cause of renal disease, age at initiation of dialysis, living with family, cardiovascular disease, and weight were assessed using Cox proportional hazard model. Median survival time was 108 months and the mortality rate was 34.8% (174 deaths). Multivariate Cox analysis showed statistically significant impact of being illiterate (p=0.03), smoking status (p=0.02), being unemployed (p=0.03), age (p<0.001), renal cyst (p=0.02), congenital disease (p=0.001), or other unspecified conditions (p=0.03) as the cause of renal diseases on survival outcome. The study also estimated the 1-, 2-, 3-, 5-, 10-, and 12-year survival rate for this cohort as 84%, 77%, 71%, 58%, 43%, and 33%, respectively (Shabankhani, Kazemnejad, Zaeri, Espahbodi, Ahmadi & Mirkazemi, 2016).

In a retrospective study by Ahmad and Shahzad in 2015, the survival rate of a sample of 40 patients receiving dialysis in two hospitals in Lahore, Pakistan and the influence of different risk

factors on outcome were analyzed. The survival distribution of factors including age (classified as "<=50 years" and ">50 years") and comorbid factors (classified as none, peripheral vascular disease (PVD), hypertension, chronic respiratory disease, hepatitis, diabetes, Ischemic Heart Disease (IHD), more than one diseases) were extracted using log rank (Mantel-Cox). At 5% significance, the survival distribution of age (p=0.012) and comorbid factors (p=0.008) were statistically significantly different. Multivariate Cox regression analysis demonstrated the statistically significant impact of Body Mass Index (BMI) (p=0.026), serum albumin (p=0.024), and family history of diabetes (p=0.001) on survival. However, the hazard of the variables in the survival of patients was not the same as the family history of diabetes (HR=0.001, 0.008 for type one and two respectively), and BMI (HR=0.88) reflected less hazard than serum albumin (HR=14.796) (Ahmad & Shahzad, 2015). These findings revealed the extreme vulnerability of dialysis patients compared to the general population.

2.8. Factors associated with mortality among dialysis patients

When commencing dialysis, several important factors should be taken into account by clinicians. These variables can be grouped into demographics, type of modality and comorbid conditions and physiology indicators.

2.8.1. Demographic characteristics

Demographic factors such as age, gender, BMI and ethnicity/race that affect survival are still only partially understood among patients with renal problems.

Age: Older age is considered as a prognostic factor for poor clinical outcome in incident dialysis patients (Sayin et al., 2013; Tonelli et al., 2006; Klarenbach, Tonelli, Chui, Manns BJ,

2014; Ryu et al., 2015; Shabankhani et al., 2016; Thijssen, Usvyat & Kotanko, 2012). According to Thijssen et al. (2012), HD patients aged 65 years old and above have a six times higher risk of mortality relative to general population. In this study age was strongly indicated to be significant in specific time periods after starting HD (p<0.0001, 95% CI, 1.018-1.046). Similarly, Shanbankhani et al. (2016), found that age is highly associated with mortality and poor survival prognosis among hemodialysis patients (HR=1.033, p<0.001). In a recent Canadian study, elderly patients (65 years old and above) experienced increased risk of mortality in both PD and HD group of patients (HR= 1.27, 1.41, 95% CI, 1.04-1.26, 1.04-1.27, respectively) (Yeates et al., 2012). In keeping with these findings, 1-year increase in age increased risk of death of Korean dialysis patients with the hazard ratio of 1.05 (95% CI, 1.05-1.06, p<0.001) (Ryu et al., 2015).

Gender: Role of gender as an independent prognostic factor for mortality is inconclusive among dialysis patients. Thijssen et al. (2012), found significant impact of gender on mortality only in certain time periods after initiation of dialysis (p<0.0001, 95% CI, 1.068-2.16). The findings of this study reflect vulnerability of male sex to mortality. However, Yeats et al. (2016), indicated that female gender is highly correlated with mortality for both age groups including 18-64 and above 65 years old among Canadian dialysis patients (HR= 1.1, 1.27, 95% CI= 0.98-1.25, 1.04-1.26, respectively). While in Korean dialysis population gender is not considered as a risk factor for death, recent comprehensive investigation of dialysis patients in South Korea revealed that female sex was associated with decreased risk of mortality (HR=0.85, 95% CI= 0.78-0.92, p<0.001) (Ryu et al., 2015). In some studies, gender does not contribute to death in dialysis patients. For instance, survival analysis of incident HD patients in Iran revealed that gender is not associated with mortality (HR=0.45, p=0.09). A survival analysis of 500 HD patients in

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Mazandaran, Iran using three hospitals during a 6-year study period demonstrated non-significant effect if gender on mortality (HR=0.44, p=0.09) (Shabankhani et al., 2016).

BMI: Numerous studies have attempted to investigate the impact of BMI on survival of patients undergoing dialysis. Existing evidence reveals that patients with high BMI are more prone to ESRD compared to the general population. Therefore, an increase in prevalence of obesity among ESRD patients requiring dialysis is becoming the focus of epidemiologists' research (Hsu, McCulloch, Iribarren, Darbinian & Go, 2006). It is reported that mean BMI has been increased in some countries. For example, among American incident ESRD patients, the mean BMI increased to 27.5 kg/M2 in 2002-2007 from 25.7 kg/M2 in 1995 (Kramer et al., 2006). Given this background, while the general population is encouraged to lower their BMI, incident dialysis patients are more likely to survive when their BMI is higher. It can be explained by two underlying reasons: first, high prevalence of malnutrition among dialysis patients (Badve et al., 2014). Malnutrition-inflammation syndrome (MIS) is one of the extremely common problems among dialysis patients and a possible risk factor for mortality (Kalantar-Zadeh, Kopple, Block & Humphreys, 2001). Nutrition loss through dialysis process, oxidative and carbonyl stress, existence of comorbid conditions, low nutrient intake and anorexia owing to loss of appetite, are all counted as potential causes of MIS (Kalantar-Zadeh, Ikizler, Block, Avram & Kopple, 2003).

Dialysis risk paradox refers to paradoxical relationship between mortality and several factors such as BMI, blood pressure and serum albumin (Speakman & Westerterp, 2010). Numerous studies have reported the survival advantage of high BMI over low BMI for dialysis patients. The systematic review of literature on the association between survival and BMI from 1982 to 2002 revealed improved survival outcome for those with high BMI (Salahudeen, 2003).

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Furthermore, these findings are consistent with those reported by Badve et al., (2014). This large registry study showed that higher baseline BMI (i.e., 28-34 kg/m2 for HD patients and 34-37 for PD patients) is associated with better survival outcome. In addition to baseline-BMI measurements, the association of time-varying BMI for both groups of PD and HD with mortality has been examined. It was concluded that time-varying measures of BMI were also significantly affecting mortality in both HD and PD patients (Badve et al., 2014). Another study involving Taiwanese population undergoing hemodialysis, found survival disadvantage of low BMI (i.e., less than 18.5 kg/m2) (Huang, Cheng & Wu, 2008). In the cohort of 109,605 maintenance HD patients, both obesity (BMI>30 kg/m2) and morbid obesity (BMI>40 kg/m2) were associated with longer survival (Ricks et al., 2011). It is worthwhile to mention that this association appeared to be more evident in blacks and the weakest in Hispanic maintenance HD patients relative to non-Hispanic patients. In fact, the survival benefit of obesity was more prominent in this ethnic group. These findings represent the protective but differential role of high BMI across different ethnic groups (Ricks et al., 2011).

However, recent studies have highlighted the limitations of BMI in the dialysis population as a reflection of body composition. There is uncertainty regarding which components of body composition (i.e., fat and body mass) are associated with survival outcome. As a result, it is challenging to quantitatively understand which components of body composition can affect survival in dialysis patients.

Race: Reports on role of racial and ethnic differences in survival of dialysis patients remains controversial. In US, the lifespan for black people is 4-5 years less than their white counterparts due to worse economic status, genetic differences affecting development of some diseases, differences in income and education, cultural disparities in the health behaviors and attitudes as

well as poorer access to care settings (Kochanek, Xu, Murphy, Miniño & Kung, 2002; Powe, 2008; Wong, Shapiro, Boscardin & Ettner, 2002). However, on the last stages of CKD better survival is reported for black patients over white patients (Jolly et al., 2011). Particularly in dialysis patients, a lower annual mortality rate (18%) is observed among black patients than non-Hispanic whites (23%) (Collins et al., 2005).

In the analysis of DaVita maintenance HD patients for the duration of 6 years, lower mortality rates are observed among black and Hispanic dialysis patients compared to non-Hispanic whites (Ricks et al., 2011). Along with this finding, Bradbury's retrospective sample from the dialysis outcomes and practice pattern study (DOPPS) in US found that white race is among the significantly elevated risk factors for mortality during the first 120 days after dialysis initiation. In the subsequent 121 to 365 days after dialysis, white race remained as a strong predictor for mortality (Bradbury et al., 2007). The finding of this study about the strength of white race and old age as mortality risk factors is consistent with some other studies involving prevalent hemodialysis patients (Goodkin et al., 2003; Ma, Ebben, Xia & Collins, 1999).

In a more recent analysis of the national United States Renal Data System (USRDS), observed mortality rate in the black population was lower compared to the non-Hispanic white group. The exception only applies to the youngest sub-population (18-30 years) in which survival is longer relative to their non-Hispanic white counterparts (Yan et al., 2013). There are a few reasons explaining the commonly cited survival advantage of blacks compared to non-Hispanic whites particularly in the older age group. Although the reasons are not well-defined, they may justify the phenomenon. These consist of different inflammatory responses (Crews, Sozio, Liu, Coresh & Powe, 2011), different cultural adaptation in chronic conditions (Norris, Kalantar-Zadeh & Kopple, 2011), different delays in time to transplantation (Hall YN, Choi AI,

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Xu P, O'Hare AM, Chertow, 2011), healthier nutritional and inflammatory status (Streja et al., 2011) and being treated with active vitamin D (Kalantar-Zadeh et al., 2010). Additionally, many studies provide strong evidence regarding survivorship biases due to receiving less pre-ESRD care among black population (Bethesda, 2011).

2.8.2. Type of modality

Given the wide prevalence of ESRD and growing economic burden of dialysis on health care systems, dialysis modality choice becomes a momentous issue. Evidence regarding the survival comparative effectiveness of HD and PD should be interpreted cautiously due to potential biases. Lack of randomized controlled clinical trials and mainly prospective study design provide information on the effectiveness dialysis modality rather than on causality relationships between modality and mortality (Yang et al., 2015).

In order to explore the existing differences between two treatment techniques among incident dialysis, fourteen relevant studies published in PubMed across the last ten years were reviewed in January 2017. The specific aim of this review was to analyze the impact of modality on mortality and compare different modalities outcome. Two primary research questions addressed by the review were focused on the independent variables included in the survival model, corresponding association with survival outcome, significant variables affecting survival as well as the outcome comparison for the two modalities. The details about the result of the review including, context data, quantitative and qualitative findings, survival outcome distribution, executive summary of evidence regarding survival outcome for two modalities, and

cohort summary are presented in the Appendix A, B, C, and D. In what follows, a brief summary of the findings of the included studies will be discussed.

Obtained results from the aforementioned review on assessing the survival outcome differences in HD and PD modalities were inconclusive. Of the 14 studies, 35% (n=5) reported similar outcomes for PD and HD (Huang et al., 2008; Madziarska et al., 2013; Lee, Sun & Wu, 2009; Wang et al., 2016; Andrikos, Tseke, Balafa & Pappas, 2008). A further 35% of the studies revealed superior outcome of PD over HD (Yeates et al., 2012; Sood et al., 2012; Serafinceanu, Neculaescu, Cimponeriu, Timar & Covic, 2014; Marshall et al., 2015; Choi et al., 2013). In one Canadian study by Sood et al. (2012), the survival outcome of PD was superior for both group of Aboriginal and Caucasian dialysis patients relative to HD. Similarly, Serafinceanu et al. (2014) found that hemodialysis as a first/single technique for RRT, is associated with increased risk of mortality. Choi et al. (2013), likewise found that patients under 65 years without diabetes have a better survival under PD than HD. In contrast, the final 30% (n=4) of studies demonstrated better survival outcome for patients undergoing HD treatment technique relative to PD (Yang et al., 2015; Kim et al., 2014; Wang et al., 2013; Sens, Schott-Pethelaz, Labeeuw, Colin & Villar, 2011).

2.8.3. Comorbid conditions

It is well-established that Cardio Vascular Disease (CVD) and diabetes are the most important co-exiting conditions that predict worse outcomes for dialysis patients (Miskulin et al., 2009; Beddhu, Bruns, Saul, Seddon & Zeidel, 2000; Hemmelgarn, Manns, Quan & Ghali, 2003; Keane & Collins, 1994; Rostand, Kirk & Rutsky, 1982). Charlson Comorbidity Index (CCI) is one the frequently used scores in the studies to measure the impact of various comorbidities on

mortality (Miskulin et al., 2009). A number of studies have shown that increased in CCI is correlated with adverse outcomes among dialysis patients such as reduced quality of life, increased costs and mortality (Fried, Bernardini & Piraino, 2001; Beddhu et al., 2000). However, a validation study of CCI on ESRD patients indicated that since this score is designed for general population, the assigned weights do not generalize to the dialysis group of patients (Hemmelgarn et al., 2003). In a study by Goodkin et al. the correlation of various comorbid conditions and mortality was examined among hemodialysis patients in different geographic locations (Goodkin et al., 2003). Consistent with a number studies, Coronary Artery Disease (CAD), Congestive Heart Failure (CHF), cardiomegaly, other cardiac diseases, diabetes mellitus, Peripheral Vascular Disease (PVD), cerebrovascular disease, lung disease, cancer, HIV infection, gastrointestinal bleeding, neurologic disease, psychiatric disease, cellulitis/ gangrene, hepatitis, and smoking are significantly associated with poor outcome (Goodkin et al., 2003, Keane & Collins, 1994; Fried et al., 2001). Similarly, Miskulin et al. (2009), indicated that aforementioned comorbidities add independent prognostic information when clinical indicators and laboratory values are included in the model. Indeed, seventeen included comorbid conditions had more discriminatory power for survival compared to laboratory and clinical indicators (Miskulin et al., 2009).

While these comorbidities are considered as strong predictors of mortality, the impact of hypertension as one of the most important risk factors for cardiovascular diseases on survival is still inconclusive (Rostand et al., 1982; Mazzuchi, Carbonell & Fernández-Cean, 1982; Rahman, Fu, Sehgal & Smith, 2000). Goodkin et al., (2003) also revealed a 26% decreased risk of mortality among patients with hypertension. Similarly, the protective role of high blood pressure in the pre-dialysis stage was also confirmed in some other studies previously (Besarab et al., 1998; Iseki et al., 1997).

Diabetes: Survival among diabetic dialysis patients is inferior to nondiabetic dialysis patients (Liem, Wong, Hunink, Charro, & Winkelmayer, 2007). There are several studies in the literature that have analyzed the impact of diabetes on survival. For example, a recent review focusing on the evaluation of dialysis diabetic patients' survival showed that both HD and PD diabetic patients had lower survival than those without diabetes (Ghaderian, Hayati, Shayanpour & Beladi, 2015). In a large international study by Schroijen et al. in (2013), the survival of dialysis patients with the history of diabetes as a comorbid condition was lower than those without the diagnosis of diabetes (HR=1.25, 95% CI=1.14-1.38). Similarly, retrospective survival analysis of 897 HD patients in a duration of 4 years in India, indicated that diabetes as a comorbidity is associated with lower survival rate (HR=1.73, p<0.001) (Vijayan et al., 2016). Likewise, the analysis of large-scale cohort from the Italian Dialysis and Transplantation registry using Poisson regression indicated the strong association of diabetes with excess mortality (Relative Excess Risk (RER) = 2.91, 95 % CI, 2.5-3.38) (Nordio et al., 2012). In a survival comparison of HD and PD patients in a registry-based data in Taiwan diabetes was significantly associated with survival outcome (adjusted HR=1.99, p<0.001) (Wang et al., 2013). A systematic review aiming at estimation of the relative risk of death associated with specific characteristics of dialysis patients was conducted analyzing 24 studies (Joanna, Gore & Firth, 1999). Using quantitative techniques in this review revealed that the relative risk of mortality associated with the presence of diabetes as a comorbid condition was 1.91 (p<0.0001). Many factors contribute to the poor prognosis of diabetic patients on dialysis such as presence of cardiovascular disorders, foot ulcer and vascular access problems due to susceptibility to infections, etc. (Schroijen et al., 2013). In contrary to the adverse impact of diabetes on survival outcome of dialysis patients, there are some studies that highlighted the insignificant impact of diabetes on mortality. For instance, survival comparison

of HD and PD patients with the presence of Congestive Heart Failure (CHF) in France did not show any significant impact of both types of diabetes on death (diabetes type 1: HR=1.11, p=0.11), (diabetes type 2: HR=1, p=0.99) (Sens et al., 2011). Similarly, in a single center retrospective study in Germany, diabetes was found as an insignificant predictor of mortality (Koch, Hollenbeck, Trapp, Kulas & Grabensee, 2006).

Hypertension: In ESRD population treated with HD and PD, the prevalence of hypertension is significantly high and often poorly controlled (Georgianos & Agarwal, 2016). The potential impact of elevated blood pressure on the occurrence of cardiovascular or cerebrovascular events has been well established in general population (Lim et al., 2012; Perkovic, Huxley, Y, Prabhakaran & MacMahon, 2007). Unlike this linear relationship between the blood pressure and mortality in general population, some reports indicate a paradoxical association between hypertension and survival outcome in dialysis patients (Kalantar-Zadeh, Kilpatrick, McAllister, Greenland & Kopple, 2005). This phenomenon referred to as "reverse epidemiology" confirming the role of hypertension as a protective feature that is associated with greater survival in dialysis population (Kalantar-Zadeh K, Block G, Humphreys MH).

Among chronic dialysis patients, pre-dialysis and post-dialysis recordings of blood pressure display a U-shape association between hypertension and mortality. To demonstrate, low and high blood pressures are associated with higher mortality in this group of patients (Zager et al., 1998). In a retrospective large sample study conducted by Zager et al. (1998), a U-shape relationship between Systolic Blood Pressure (SBP) and mortality was found. In a duration of 5 years follow-up time, 433 HD patients were analyzed using Cox proportional hazard regression with time-varying covariates. Exploring the association between SBP and Diastolic Blood Pressure (DBP) on cardiovascular mortality in this population, demonstrated the significant

impact of low blood pressure on the increased risk of mortality. In both pre- and post-dialysis, low SBP identified as less than 110 mm Hg was strongly associated with the risk of cardiovascular mortality. Similarly, post-dialysis, SBP greater than 180 Hg (RR=1.96, p<0.015) and DBP above 90 Hg (RR=1.73, p<0.05) significantly increased the risk of cardiovascular mortality. Additionally, there was no relationship between both SBP and DBP and cardiovascular mortality, before initiating HD.

On the other hand, there are several studies in the literature, highlighting the role of hypertension as a risk factor for increased risk of cardiac events and death. According to Foley et al. (1996), even moderate hypertension worsened the clinical outcome in both HD and PD dialysis patients particularly among those without a history of cardiac events. Similarly, a study by Charra et al. (1992), showed that excellent survival results in 445 HD patients were attributable to improved blood pressure control. A retrospective cohort study of Indonesian Renal Registry applying time-dependent cox regression in the duration of 2007-2012 indicated the significant effect of diabetes and hypertension on mortality among hemodialysis patients with the hazard ratio of 1.17 and 1.04, respectively (Purnama, Riono & Farid, 2015).

A study by Lucas et al., (2003) investigated the effect of hypertension in survival outcome of 184 HD patients before commencing dialysis. Conventional Cox proportional hazard model was utilized adjusting for age, sex, albumin, vascular calcification, history of hypertension and comorbidity. History of hypertension was defined as the average of three blood pressure measurements per year during the outpatient's study follow-up. Based on this categorization, three groups were identified as the history of hypertension: normotensive, controlled hypertensive with therapy and uncontrolled hypertensive despite treatment. The threshold for normal or controlled hypertension was considered less than 140/90 mm Hg. Comorbidity

(HR=1.95, p=0.003) and uncontrolled hypertension (HR=1.79, p=0.01) were highly associated with all-cause mortality. For cardiovascular mortality, uncontrolled hypertension before initiating dialysis was an independent risk factor (HR=2.93, p<0.05).

There are also some studies that found the nonsignificant effect of hypertension on the survival of dialysis patients. For example, in a prospective study by Tong J et al., in 2016 survival analysis of 591 dialysis patients in two centers revealed nonsignificant effect of hypertension as a comorbidity and SBP on all-cause mortality. In this study presence of hypertension as a comorbidity identified if the patient was under antihypertensive medication or had two measurements for blood pressure in different occasions greater than 140/90 mmHg. In contrast, the DBP was found as an independent risk of mortality (HR=0.976, p=0.015).

Cancer: History of cancer as one of the common comorbidities can be associated with adverse outcome among chronic dialysis patients. For example, in a study by Floege et al in (2015), history of cancer was found as to be a significant risk factor for 1 and 2- year mortality among incident HD patients (HR=1.75, 95% CI=1.49-2.05). Similarly, survival analysis of 35, 664 dialysis patients in Taiwan indicated the significant impact of cancer on survival outcome (HR=1.25, p<0.001) (Wang et al., 2013). In spite of the significant impact of cancer on mortality in dialysis population, some other studies indicated the nonsignificant impact of this comorbidity on the outcome. In a retrospective study by Béchade et al. (2017), survival outcome of incident chronic dialysis patients with a previous diagnosis of cancer was evaluated. Using KM survival curves and stratified Cox model, survival of patients with and without cancer was not different and the history of cancer was not associated with death (HR=0.96, p=0.8). Survival analysis population-based data of 975 HD and PD patients with the history of prior stroke in Taiwan,

indicated that cancer was not associated with survival (HR=0.62, 95% CI=0.28-1.37) (Wang et al., 2016).

Stroke: Like other comorbidities such as diabetes, stroke is also common among patients undergoing chronic dialysis but how it is associated with survival outcome is still unknown (Wetmore, et al., 2014). Retrospective analysis of 69, 371 long-term dialysis patients using a semi-Markov model revealed that dialysis patients experienced higher mortality after ischemic and hemorrhagic stroke. The corresponding adjusted HRs for ischemic and hemorrhagic stroke were 1.7 ($p<0.0001$) and 1.3 ($p<0.001$) at 36 months (Wetmore, et al., 2014). In a prospective cohort study of 591 dialysis patients using multivariate Cox model, stroke was an independent predictor of all-cause mortality among dialysis patients with the presence of CVD (HR=4.57, $p<0.001$) (Tong et al., 2016). Another study in Taiwan also assessed the risk of mortality among 5672 HD patients with and without the history of stroke. Using multivariate Cox model in this study indicated that history of stroke at the time of starting dialysis is an important predictor of all-cause mortality among incident HD patients (HR=1.36, $p<0.001$) (Chien et al., 2013). In contrary to these findings, some other studies did not find any significant impact of stroke on survival outcome such as an observational study by Cherukuri & Bhandari in 2009. In this prospective study using data from a dialysis center in the UK, history of stroke was not associated with survival outcome (Cherukuri & Bhandari, 2009).

Cardiac disease: Coronary Artery Disease (CAD) is the most common type of cardiac disease and as a comorbid condition contributes to the increased risk of mortality among dialysis population (Chou & Fang, 2013). Moreover, the presence of Myocardial Infarction (MI) as a comorbidity can also worsen the survival outcome of dialysis patients. For example, analysis of 15,245 incident HD and PD patients in a 3-year study showed that MI was associated with

increased risk of early mortality among younger patients (i.e., <45) in this population (Odd Ratio=8.8, 95% CI= 4.2-18.6) (Soucie & McClellan, 1996). Survival analysis of 35, 664 PD and HD patients in a duration of 10 years follow-up found the significant impact of CAD on survival outcome (HR=1.14, p<0.001) (Wang et al., 2013). Survival comparison of chronic HD patients with and without the history of stroke in Taiwan revealed that presence of CAD was associated with increased risk of all-cause mortality in this population (HR=1.88, p=0.003) (Chien et al., 2013). Another study by Goodkin et al. (2002), using DOPPS registry data found CAD as a significant predictor of mortality (RR=1.31, p=0.001).

In contrast, some other studies in this context showed that pre-existing CAD was not associated with survival outcome in dialysis population. A prospective study in Japan using 947 HD patients' data examined the predictive value of various variables for mortality. Appling Cox model in this study indicated that CAD was a nonsignificant predictor of mortality among long-term HD patients (HR=1.46, p=0.290) (Ajiro et al., 2007). This finding was in line with others such as studies by Lawton et al. (2015), and Andrikos et al. (2008), in which CAD was an insignificant variable in the survival analysis of dialysis patients.

Lung disease: There is an increasing evidence that presence of lung disease disorders could lead to an adverse outcome in dialysis population. For instance, analyzing HD patients' data in DOPPS registry by Goodkin et al., in 2002 indicated the increased risk of mortality in the presence of lung disease (RR=1.53, p<0.0001). Likewise, survival analysis of HD and PD patients with the presence of CHF in Taiwan showed that chronic lung disease at the baseline was significantly associated with mortality (HR=1.09, p=0.17) (Wang et al., 2013). In contrast to these findings, some studies found the insignificant of lung disease on survival outcome. For example, a very recent multicenter prospective cohort study in Korea by Park et al. (2018),

demonstrated the non-significant impact of chronic lung disease history on survival among Korean dialysis population (HR=1.24, p=0.2). Similarly, survival outcome comparison between HD and PD patients in France revealed that presence of chronic lung disease did not impact the survival (HR=1.09, p=0.17) (Sens et al., 2011).

2.8.4. Mental health disorders

Several investigators showed that poor mental health at the time of starting dialysis can impact survival of dialysis patients. For instance, depression as the most common type of psychological disorder in dialysis patients is associated with a high risk of mortality in this population (Fischer, Porter & Lash, 2013). Chilcot et al., in 2010 analyzed 160 incident HD and PD patients from three renal centers in the UK in a prospective study. Using Cox regression model adjusted for other comorbid conditions illustrated that depression score was a significant predictor of mortality (HR=1.07, p=0.002). Moreover, in an additional adjusted Cox model, the severity of depression symptoms soon after the dialysis initiation was also an independent predictor of survival outcome (Chilcot et al., 2010). In another prospective study in Southwestern Pennsylvania survival analysis of 66 PD patients revealed that depressive patients experienced a higher risk of death (Einwohner, Bernardini, Fried, & Piraino, 2004). Examination of different factors such as psychiatric disorders, including dementia, depression and bipolar and their association with survival outcome was conducted by Goodkin et al., in 2003 among HD patients. Analyzing DOPPS registry data as an observational prospective study indicated significant impact these psychiatric disorders on survival outcome in both multivariate and univariate analysis (univariate: RR=1.64, p<0.0001; multivariate: RR=1.3, p<0.0001).

A retrospective cohort study analyzing 272, 024 incident dialysis patients in the United States Renal Data System (USRDS), estimated the risk of death among those diagnosed with dementia at the baseline. Using Cox regression model showed that presence of dementia at the time of commencing dialysis is an independent risk factor for mortality (HR=1.91, p<0.001) (Rakowski, Caillard, Agodoa & Abbott, 2006). Another large registry-based study using DOPPS data also highlighted the significant impact of dementia on adverse outcome among HD patients (RR=2.01, 95% CI=1.57-2.57) (Kurella, Mapes, Port & Chertow, 2006).

In spite of significant findings on the impact of mental health factors on survival of dialysis patients, there are some early studies that found an insignificant association of these factors and the survival outcome. For instance, analyzing 97 HHD and PD patients revealed that existence of depressive symptoms was not associated with survival outcome (Devins et al., 1990). Similarly, survival analysis of 295 incident HD dialysis patients in a prospective, longitudinal study indicated the non-significant impact of depression on mortality (Kimmel et al., 1998).

Some other further studies also showed this insignificant association of depression and mortality in dialysis population such as studies by Kimmel et al. in 2000 and Boulware et al. in 2006. Additionally, comprehensive examination of depressive symptoms and their impact on mortality among 323 HD patients by Fan et al. (2014), revealed the attenuated association adjusted for other comorbidities.

2.8.5. Physiology indicators

Laboratory values such as albumin, hemoglobin, potassium and phosphorus are among the important determinatives for mortality not only at the time of commencing dialysis but also during the course of maintenance dialysis. In an observational study analysing chronic dialysis

patients' data over 14 years, laboratory values within three to six months after dialysis initiation whether HD or PD were considered. The impact of albumin, serum phosphate, and calcium on long-term survival outcome were explored retrospectively. By grouping patients into two different groups based on the threshold value of serum phosphorus (above and below 1.8 mmol/L), only18 percent of the patients had the value above this level. The results of the study indicated that the five-year survival of these patients was 48.4% compared to those with a serum phosphorous<1.8 mmol/L with the survival rate of 58.6%. For albumin, five-year survival was 65.1% for patients that have the value of above 35 g/L versus 37.7% for those with the value below the threshold (p<0.001, 95%CI=0.98-1.25). In brief, hypoalbuminemia and hyperphosphatemia were strong predictors of all-cause mortality in this study. It was also concluded that low serum albumin along with other factors such as low BMI and low blood nitrogen urea, are considered as signs of under-nutrition leading to reduced survival (Phelan, O'Kelly, Walshe & Conlon, 2008).

In a retrospective observational study by Mafra et al. (2007) in a five-year follow-up, the effect of low BMI and serum albumin on increased risk of mortality were examined using a Cox model (86). In the analysis, two categories of patients in terms of level of albumin were defined (below and above 3.5 mg/dl). The results of the study showed that lower levels of BMI(<19kg/M2) and albumin (<3.5 mg/dl) are the most significant predictors of increased risk of mortality among hemodialysis patients. The risk of all-cause mortality was 2.63 times higher in the category of lower albumin (p<0.001, 95%CI=01.05-1.25) and 1 g/l increase in serum albumin was associated with improved survival which was significantly reduced hazard of mortality (HR= 0.97, p<0.001) (Mafra et al., 2007). Similarly, in a retrospective descriptive study, the impact of BMI and albumin were evaluated among 204 African-American

hemodialysis patients. The research demonstrated that albumin<3.2 g/dl is one of the strong predictors of mortality. Using the mean value of albumin in the logistic regression model demonstrated that significant impact of it on survival (p<0.001, 95%CI=1.06-1.35) (Feingold, Adams, Penprase & Tubie, 2007).

The findings of the aforementioned studies were consistent with Bradbury et al. (2007) and Kalantar-Zadeh et al. (2005) surveys indicating that low albumin level is one of the powerful risk factors for mortality in HD patients. In the first study, a retrospective cohort from DOPPS in US were used to explore the most significant predictors affecting survival. Preliminary analysis of the first study demonstrated that 40% of the patients had albumin below 3.5 g/dl (Bradbury et al., 2007). In the second study, all-cause and CV mortality was highly influenced by a decline in serum albumin over the course of six months. For the same duration, improved survival outcome was correlated with increased level of serum albumin of >= 0.3 g/dl with HR=0.78; 95%CI= 0.71-0.86 (Kalantar-Zadeh et al., 2005).

More recently for peritoneal dialysis patients, the impact of albumin on mortality was assessed in a prospective, single cohort of 30 patients over five years by Terawaki et al. in 2012. In this study, the correlation of serum albumin and incidence of serious CVD was examined. The results of this study revealed that a lower level of reduced albumin is significantly correlated with serious incidence of CVD and corresponding mortality (Terawaki et al., 2012).

As mentioned before, survival outcome is also influenced by different physiology indicators such as hemoglobin and phosphorus as equally important variables. Hyperphosphatemia, control, is considered as one of the important integrals of chronic kidney disease management. Kestenbaum et al. (2005) demonstrated that elevated serum phosphorus is significantly associated with increased risk of mortality. Similarly, another study indicated that decrease in

serum phosphorus in patients with baseline values of > 5.2 mg/dL is correlated with improved survival outcome (Fernández-Martín et al., 2015). However, two studies conducted by Tentori et al. (2007) and Thijssen et al. (2012) respectively, found insignificant impact of phosphorous on mortality compared to other laboratory predictors. In the study by Thijssen et al. (2012), the hemoglobin levels after initiation of HD was significantly associated with mortality. In accordance with these findings, a study from UK Renal National Registry cohort, indicated that hemoglobin is one of the powerful predictors of mortality (Wagner et al., 2011).

Chapter 3: Study rationale and research questions

3.1. Clinical and public health implications

High mortality is reported among dialysis patients, particularly within the first months after dialysis initiation. According to Bradbury et al. (2007), 20% of the total deaths occur in the first year after dialysis initiation. This high rate of mortality and the corresponding reasons have drawn great attention from physicians and clinical researchers worldwide. However, the reasons for this high rate still remain unclear and require full exploration.

 The overall aim of this study was to (1) estimate the survival rate of incident chronic dialysis patients in the regional renal program at Grand River Hospital (GRH), (2) determine whether the survival outcome differed in Hemodialysis (HD) and Peritoneal Dialysis (PD) patients and, (3) identify significant variables that affect survival outcome.

The essential knowledge gained through this investigation is intended to help dialysis patients enhancing individual outcome by improving modifiable risk factors. Moreover, the results of this study will contribute to future planning and organizing of renal dialysis programs such as the Ontario Renal Network (ORN) and British Columbia Renal Agency (BCRA). Based on the knowledge extracted about differences between patients who survived and those who did not during the same period, physicians and clinical teams may be better able to predict potential problems before they arise. Extracted prognostic information will help patients share in their treatment decisions rather than having them dictated.

3.2.   Research questions and objectives

3.2.1. Primary research questions

1) What is the current survival rate among dialysis patients receiving care in GRH?

2) Does the survival outcome differ for patients receiving HD and PD?

3) What are the significant predictors for the survival outcome of chronic dialysis patients?

3.2.2. Study objectives

The objectives of the proposed study are to investigate the following in a retrospective cohort of chronic dialysis patients in GRH:

a) The overall survival rates, by:

- Age group, gender, and type of modality

b) Whether the survival outcome differs among patients undergoing PD and HD.

c) The significant predictors that affect survival outcome.

Chapter 4: Methods

4.1. Data source

The Ontario Renal Network (ORN) consists of 26 regional renal programs, each offering a variety of treatment services to patients suffering from Chronic Kidney Disease (CKD) in Ontario. Grand River Hospital's (GRH) renal program, recognized as one of the largest community hospital regional dialysis programs (i.e., the eighth largest program) in Ontario, provides acute and chronic kidney disease services within Waterloo Wellington. This renal program includes in-center, home and satellite Hemodialysis (HD) units, as well as out-patient Peritoneal Dialysis (PD) and chronic kidney disease clinics. To demonstrate, these services consist of "early identification, delay of disease progression, inpatient dialysis, (home HD and PD), modality selection, acute HD and pre-transplant preparation" (Waterloo Wellington Regional Renal Program, Renal Plan 2015-2019)[1]. Satellite units in this renal program provide services for patients in Kitchener, Guelph and Palmerston regions. There are 74 HD stations available in the Waterloo Wellington regional program. In total, over 500 patients receive dialysis and more than 140 home-based dialysis patients live independently in this regional renal program.

4.2. Study population

Inclusion criteria: Male and female adult patients (>18 years old) who began chronic dialysis treatment (at home or hospital) between January 1th, 2012 and September 30th, 2017 in

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the renal program at Grand River Hospital were eligible for the analysis. Patients who underwent dialysis for more than 30 days were considered chronic. This definition is extracted from ORN definition[1] (Lattouf & Ricketts, 1986).

Exclusion criteria: In this study, patients who started dialysis on an emergency basis or acute dialysis (with the duration from first to last dialysis being less than 30 days) and those having only one dialysis session were excluded. An exception was applied to those discharged/recovered or withdraw from treatment, but who later started chronic dialysis. For this group, the first day of dialysis was estimated from the initiation of chronic dialysis. In order to prevent lead time bias, patients who were undergoing dialysis before the study's start date (i.e., prevalent patients) were excluded from the study.

4.3. Ethics

Ethics approval was obtained from the Human Research Ethics Board of the University of Waterloo (ORE # 22069). The study was also approved at the GRH by the Tri-Hospital Research Ethics Board (THREB) (THREB File # 2016-0619), along with the waiver of "the requirement to obtain patient informed consent". The ethics approval forms can be found in the Appendix E.

4.4. Data extraction

Patient-information reporting platforms, including Nephroport and Nephrocare for the renal program at GRH, as well as clinical chart reviews of participants' electronic files in ClinicalConnect™ were utilized for data extraction. All the required Protected Health Information (PHI) protection measurements were applied strictly during data extraction, to ensure appropriate access control to databases and the crosswalk file. Medical Record Numbers

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[1] Ontario Renal Network (ORN)- Ontario Renal Plan. Retrieved at:
http://www.renalnetwork.on.ca/ckd_data/accountability_to_patients_data/techinfo/ - .W1Yw2K0ZP-Z

(MRNs) were used to identify relevant patient records and were identified on the data collection forms as Subject Identification Numbers (Subject_IDs). Random Subject_IDs and Encounter Identification Numbers (E_IDs) were generated to identify each patient and encounter. Final mapping information across Subject_IDs, MRNs and E_IDs in the crosswalk file were stored on a secure computer in GRH.

De-identified extracted data were entered in Excel sheets for the analysis. Two graduate students checked the validity of extracted data by randomly selecting patients and comparing the values across Nephrocare, ClinicalConnect™, and the extracted data file. Preliminary descriptive analysis in two separate analyses conducted, by the same two graduate students, also cross-validated the extracted data file. Furthermore, each patient's clinical records and notes in the ClinicalConnect™ were reviewed.

4.5. Data collection steps

In the first step, data for the included variables were extracted from the two patient-information platforms in the renal program at GRH. This step lasted from February 2017 to May 2017. Subsequently, between June and October 2017, the same students reviewed each patient's record in Nephrocare in order to check for the validation and completeness of the extracted data. All the variables included in this study were recorded in an Excel file. For validation and data entry quality assurance, a few patients were randomly selected and checked. In the next step, missing values for selected variables were completed by having three graduate students review clinical notes and reports available in ClinicalConnect™. A mixture of clinical notes, assessment summary and history summaries were available in the ClinicalConnect™ for each patient. To review the most relevant reports, several strategies were adopted such as selecting reports close

to dialysis initiation and using nephrologists' assessments, discharge summaries and anesthesiologist summaries.

For reviewing the clinical notes in the last step, a few assumptions were made for the purpose of quality control assurance. For recording comorbidities, the presence of any diagnosis identified by the clinicians at the dialysis initiation was selected and used as a comorbidity, whether the patient recovered or the disease improved subsequently.

4.6.   Key variables in survival analysis:

a) Outcome variable:

The outcome variable can be represented by pairs of random variables as (T, δ). In survival analysis, the primary outcome variable is "time until an event occurs", denoted by T (Kleinbaum & Klein, 2006). The status variable, δ, indicates either the occurrence of an event or censorship for the patient. Where $\delta=1$, the patient experienced the event of interest during the study period, while $\delta=0$ means that the survival time was censored in the study period (Dietz at al., 2002). In fact, if the event did not occur during the follow-up time, the censorship was the only possibility for the patient's survival time (lost to follow-up or survived until the study end point). In this study, the starting point was defined as the time of dialysis therapy initiation, based on the date of patients' first recorded dialysis treatment. Thus, the outcome variable was measured from the dialysis initiation until death. Patients who were lost to follow-up, transferred out of the hospital or to another center, transplanted or remained in the study to the end of study period were right-censored. It was assumed that censoring was independent or non-informative in this study.

b) Independent variables:

Based on the retrospective nature of the study and the availability of the variables, as well as on the results of the literature review on significant predictors in survival, the following variables were chosen:

1) Age at dialysis initiation in years: measured from birth year at the time of starting dialysis. Age is considered as a confounder in this study as it may affect the association between various comorbidities and survival outcome.

2) Gender (male/female): 1=Male, 2=Female.

3) Myocardial Infarction (MI): (1= Yes, 0=No)

4) Cardiac disease, including Coronary Artery Disease (CAD), cardiac arrhythmia, cardiac failure, cardiac valvular disease, pericardial disease, cardiomyopathy, and congenital heart disease: (1= Yes, 0=No)

5) Cerebrovascular Accident (CVA): (1= Yes, 0=No)

6) Cancer: (1= Yes, 0=No)

7) Lung disease: (1= Yes, 0=No)

8) Diabetes: (1= Yes, 0=No).

9) Hypertension (HTN): (1= Yes, 0=No)

10) Depression: (1= Yes, 0=No)

11) Bipolar: (1= Yes, 0=No)

12) Dementia: (1= Yes, 0=No)

13) Modality: type of modality 90 days after dialysis initiation (HD=1, PD=2)

It is worth mentioning that although laboratory values were collected for this study, they were not included in the statistical analysis. The reason is that laboratory values available in the systems were not necessarily captured exactly at the time of dialysis initiation and there was a possibility that those values had been improved by starting the dialysis therapy.

4.7. Statistical analysis

Prior to the survival analysis, long data format was converted into wide format using R statistical software. A value of $p<0.05$ was considered statistically significant. All statistical analysis was conducted in R statistical software. The statistical methods used in this study are described below.

4.7.1. Descriptive data analysis

To describe and summarize the baseline characteristics of the study, descriptive analysis was performed. The frequency distributions of patients, central tendency, and dispersion were evaluated. For categorical variables, frequency and percentage were used, and continuous variables were presented as the mean and standard deviation (SD) (i.e., mean±SD). Along with a general description of the cohort, patient characteristics according to the age and the type of modality were compared, using the Chi-square test for categorical variables and t-test for continuous ones. For both tests, a two-sided p of 0.05 was used to denote the significance of comparing the HD and PD groups.

4.7.2. Kaplan-Meier survival curves

In order to analyze unadjusted survival, Kaplan-Meier (KM) survival curves were employed for different age groups, genders and types of modality. For the whole cohort, the overall survival curves were also generated. As a description of survival time in this cohort, the median survival time and probability of survival were estimated. The KM analysis is described next.

KM is one the most common estimators that deals with survival data and can be used for preliminary descriptive analysis such as median survival time calculation, as well as in creating survival curves (Bruce, Pope & Stanistreet, 2008). Information from all the observed subjects, including censored and uncensored can contribute to the KM estimator by representing any time point as a series of steps identified by the observed survival and censored times (Smith & Smith, 2003). Of note, this method is suitable when there is no assumption regarding the hazard rate (i.e., no assumption about the functional distribution of hazard rate with time). Both the median survival time and the proportion of subjects alive at a specified time can be extracted directly from the KM graph (Allison, 2010).

The KM estimator is as following:

$$S(t) = \prod_{j:t_j \leq t} \left(1 - \frac{d_j}{n_j}\right) \tag{1}$$

where d_j is the number of individuals who experienced the event of interest at time t_j, and n_j is the number of individuals who are at risk at the time of experiencing the event (since they have not yet experienced the event by that time) (Smith, T., & Smith, B., 2003).

4.7.3. Log-rank test

This statistical test was used to compare the survival time of one or more groups for the variables, including age, gender and modality type. One of the most popular methods used for evaluating whether or not KM curves are statistically different for one or more groups is the log-rank test. It is a form of large-sample chi-square statistical test that evaluates a null hypothesis. Under this hypothesis, it is assumed that "there is no difference between populations in the probability of an event at any time" (Singh & Mukhopadhyay, 2011).

To perform this statistical test, in each group, the number of observed events for each single time point and the number of expected events (number of individuals who are at risk at a given time point multiplied by the number of events at the given time point) is required. The log-rank test formula for more than two groups is as follows (Kleinbaum & Klein, 2006):

$$X^2 = \sum_{i}^{n} \frac{(O_i - E_i)^2}{E_i} \tag{2}$$

where O_i is the total number of observed events (i.e., death), E_i is the expected number of events, and n is the number of groups.

The degree of freedom for this statistical test in large sample sizes is G-1, where G is the number of groups being compared. The p-value for this statistical test is obtained from chi-square distribution tables (Kleinbaum & Klein, 2006).

4.7.4. Modeling survival data

The modeling of survival data is important for two main reasons: 1) to identify which combination of potential explanatory variables affect the hazard functions; 2) at the individual

scale, to estimate the hazard function for each patient. This estimation leads to obtaining quantities such as the median survival time, which will be a function of the explanatory variables in the survival model. For future and current patients, with particular values of the explanatory variables, the median survival rate can be estimated. Therefore, the resulting estimation could be useful in counseling patients' about their prognoses, as well as in customizing treatment plans for patients with different characteristics. Two fundamental functions are used to summarize and model the survival data: the survival function and hazard function.

4.7.4.1.   Survival function:

Obtaining survival probabilities from different values of t provides important information from survival data. The survival function (or reliability function) denoted by $S(t)$ gives the probability that an individual will survive beyond a certain point of time, t (experience the event of interest after time t).

$$S(t) = P(T > t) \tag{3}$$

T refers to a nonnegative random variable denoting the time to an event or the survival time. Since T is a continuous variable, the survival function is the complement of the cumulative distribution function, which is:

$$S(t) = 1 - F(t) \tag{4}$$

where $F(t) = P(T \leq t)$.

Thus, the survival function is the integral of the probability density function, which is $f(t)$. The survival function can be written as follows (Therneau & Grambsch, 2013):

$$S(t) = P(T > t) = 1 - F(t) = \int_t^\infty f(t)dt \tag{5}$$

4.7.4.2.   Hazard function

Survival models are often written in terms of a hazard function, which is considered as another quantity fundamental to a survival analysis context. This function is defined as follows, where Δt denotes a small interval of time. The formula for the hazard function is

$$h(t) = \lim_{\Delta t \to 0} \left(\frac{P[t \leq T < t + \Delta t | T \geq t]}{\Delta t} \right) \qquad (6)$$

While the survival function only gives a cumulative measure over time, a hazard function reveals a measure of instantaneous potential at time t for the event to occur, given that the individual has survived up to time t (Therneau & Grambsch, 2013). Unlike the survival function, which focuses on not failing, the hazard function focuses on failure, which is the event occurring.

4.7.5. Multivariate analysis

The above-mentioned statistical analyses (i.e., Kaplan-Meier and log-rank test) methods were utilized to investigate survival outcome with respect to one factor under investigation. Primarily because these methods consider only one dependent variable at a given time, the association among more than one variable in a multivariate method would be explored. Hence, a multivariate Cox proportional hazard regression was generated to determine which combination of potential explanatory variables affects the form of hazard function. This analysis was very informative because it evaluated multiple variables. For example, this model yielded the hazard ratio that gives the effect of each variable adjusted for age as a confounder in the model. In the following, there is a statistical description of the Cox model:

In order to model the time to an event, non-parametric and semi-parametric survival analysis techniques are often used. The Cox proportional hazard Model, a semi-parametric model, is

preferred over logistic models in the presence of censoring and survival data, as a logistic model ignores survival times by considering only a (0,1) as an outcome whereas the Cox model uses survival information (Kleinbaum & Klein, 2006). The Cox model specifics the survival function predicting the probability of an event at a given time *t* for given values of the predictors. This analytical method enables us to model how the risk of death depends on a number of predictors or explanatory variables. Categorical and continuous variables, either alone or in combination, are handled readily in a Cox regression model (Bruce at al., 2008). It is much more useful to employ Cox models when there are continuous variables, rather than the Kaplan-Meier approach. Cox regression coefficients and survival function shape are identified by the cohort subjects (observed subjects) (Therneau & Grambsch, 2013). The produced model can be applied to new patients who have measurements for the explanatory variables. The Cox model is usually written in terms of hazard function. The Cox proportional model identifies the hazard at time *t* for an individual with a given set of explanatory variables which follows (Kleinbaum & Klein, 2006):

$$h(t, \mathrm{x}) = h_0(t) \exp\left(\sum_{i=1}^{n} \beta_i X_i\right) \tag{7}$$

where $h_0(t)$ is the baseline hazard function (or nonnegative function of time), β is a regression coefficient, $\mathbf{X} = (X_1, X_2, \dots, X_n)$ denotes the vector of explanatory variables.

4.7.6. Variable selection

In statistics, particularly in regression analysis with a number of variables, not all variables may contribute to the response. Consequently, sometimes it is desirable to reduce the number of variables included in the final model. The purpose of variable selection is to improve model

prediction accuracy and also to make it easier to interpret (Dietz et al., 2002). In this study, a backward selection variable procedure was performed using R statistical software.

The initial Cox model started with all 13 variables included in the model, and at each step, the least significant variable (i.e., variable with the largest p-value) was removed from the model. This procedure continued until the p-values were below the critical p-value (Moore & Dirk, 2016).

4.7.7. Assumption of proportional hazard

In this study, one of the issues which needed to be assessed was the assumption of proportional hazard. The key assumption of the multiplicative hazard models is that the ratio of hazard for a given variable does not change over time. The hazard for each subject is a fixed proportion of hazards, meaning that the effect of a given explanatory variable is constant over time for all other subjects in a group (Hess, 1995). In other words, when all the explanatory variables are fixed at time 0, the hazard ratio of two subjects or individuals with the value of x_i is proportional (Dietz at al., 2002). In fact, the relative hazard for any two subjects follows this relationship (Therneau & Grambsch, 2013):

$$\frac{h_0(t)e^{X_i\beta}}{h_0(t)e^{X_j\beta}} = \frac{e^{X_i\beta}}{e^{X_J\beta}} \tag{8}$$

This relationship is independent of time and holds different subjects (i.e., i and j) for each variable.

In this study, the proportionality assumption was assessed using a Schoenfeld statistical test. This method is the most preferred and reliable one compared to other techniques such as graphical ones, because it uses a statistical method and provides a statistical test and a p-value

for a given explanatory variable (Kleinbaum & Klein, 2006). This test, originally proposed by Schoenfeld in 1982, has three main steps for implementing this statistical test. In the first step, a Schoenfeld residual for each variable in the model is calculated. Then, survival times are ranked by creating a variable (Kleinbaum & Klein, 2006). Finally, the correlation between the variables created in the first step and the ranked ones is tested in the H_0 hypothesis. Rejection of the null hypothesis indicates that proportionality is not satisfied. (Kleinbaum & Klein, 2006).

Chapter 5: Results

5.1. Dataset

A total of 723 chronic dialysis patients who started dialysis between January 1, 2012 and September 30, 2017 were included in the current analysis. During this period, death occurred in 284 patients (39.28%). Of the whole cohort, 18.4% (n=133), 9.7% (n=70), 5.5% (n=40), 4.1% (n=30), 1.1% (n=8) died in the first year, second year, third year, fourth year, and fifth year, respectively, during that period. The average follow-up time was 644 days. Of the whole deceased patients, 70 were voluntarily withdrawal patients who were also considered deceased in consulting with the clinical experts and the existing palliative care protocol in GRH. Any death that occurred after the study cut-off date of September 30, 2017 was censored.

5.2. Descriptive analysis

Descriptive analysis was conducted to describe the population characteristics during the study duration. Table 1 presents the descriptive characteristics of the full dataset (n=723) and Table 3 presents them by type of modality. Overall, most of the included patients were males (62.66%), aged on average 64.86 years old at the time of dialysis initiation. More than half were located in the two older age categories (28.77% being 65-74 years old and 28.63% being more than 75 years old). The two youngest groups of patients contained the least number of dialysis patients, with only 10.93% and 10.51% in the categories 18-44 and 45-54 years old, respectively. Patients aged 55 to 64 had the frequency of 21.16% of the whole cohort. Therefore, most of the patients were relatively old at the time of dialysis initiation.

A majority of the patients (81.88%) initially underwent HD, and the rest started PD (18.12%). The comorbid conditions at baseline, in the order of most-to-least common, were HTN

(88.8%), diabetes (63.76 %), cardiac disease (57.12%), cancer (31.54), MI (27.39%), CVA (27.11%), and lung disease (23.79%). This dataset was a healthy group of individuals in terms of psychological indicators. To demonstrate, only 5.53% had dementia, 2.49% had bipolar disorder, and 29.46% had depression.

Table 1. Descriptive characteristics of analytic sample (N=723)

Variable	Frequency (n)	Percentage
Age (Mean±SD)	(64.86±14.89)	
18-44	79	10.93
45-54	76	10.51
55-64	153	21.16
65-74	208	28.77
>75	207	28.63
Gender		
Male	453	62.66
Female	270	37.34
Modality		
HD	592	81.88
PD	131	18.12
Comorbidities		
Diabetes	461	63.76
HTN	642	88.8
Cardiac disease	413	57.12
MI	198	27.39
Cancer	228	31.54
CVA	196	27.11
Lung disease	172	23.79
Mental health disorders		
Dementia	40	5.53
Depression	213	29.46
Bipolar	18	2.49

5.3.   Baseline characteristics by age

Age was considered as the confounder in the current analysis, to describe the effect of different risk factors on survival outcome. Thus, it is important to estimate the impact of age on variables included in this study. Table 2 lists average age and Standard Deviation (SD) estimates for the variables used in describing the study cohort. Male and female patients had a similar average age (males: 65.11, females: 64.43, p=0.56). As shown below, patients without comorbidities and mental disorders were generally younger than those with such risk factors, apart from depression, bipolar and HTN. However, this association was not statistically significant for some of the variables such as CVA (yes: 65.91, no=64.46, p=0.24) and diabetes (yes: 65.62, no=63.52, p=0.08). The average age was strongly associated with five variables, in that patients without MI (yes:67.95, no:63.69, p<0.001), cardiac disease (yes:67.85, no:60.87, p<0.001), dementia (yes:74.7, no:64.28, p<0.001), lung disease (yes:68.09, no:63.85, p<0.001) and cancer (yes:66.57, no:64.07, p=0.03) were younger. Notably, bipolar (yes:51.89, no:65.19, p=0.01) and depression (yes:62.54, no:65.83, p=0.01) were also significantly associated with age but in a reverse way as patients with these risk factors were younger. In summary, all mental health disorders were significantly associated with age, while only four comorbidities were significantly associated with age. It is worth mentioning that descriptive results based on mental health disorders, may prone to underreporting issues practically among younger group of patients.

Table 2. Baseline characteristics by age

Variable	Average age	SD	P-value
Gender			
Male	65.11	14.43	0.56
Female	64.43	15.66	
Modality			
HD	64.93	14.80	0.784
PD	64.52	15.34	
Comorbidities			
HTN			
Yes	64.70	14.93	0.42
No	66.10	14.60	
Cardiac disease			
Yes	67.85	12.66	<0.001**
No	60.87	16.63	
CVA			
Yes	65.91	14.71	0.24
No	64.46	14.95	
MI			
Yes	67.95	11.64	<0.001**
No	63.69	15.80	
Diabetes			
Yes	65.62	13.78	0.08
No	63.52	16.62	
Cancer			
Yes	66.57	13.27	0.03*
No	64.07	15.53	
Lung disease			
Yes	68.09	11.96	<0.001**
No	63.85	68.09	
Mental health disorders			
Depression			
Yes	62.54	14.5	0.01*
No	65.83	14.96	
Bipolar			
Yes	51.89	19.48	0.01*
No	65.19	14.62	
Dementia			
Yes	74.7	11.63	<0.001**
No	64.28	14.87	

Asterisks denote difference between groups; *significant at 0.05 level; **significant at 0.001 level

5.4. Baseline characteristics by type of modality

Prevalence estimates for HD and PD modalities were calculated within the entire chronic dialysis patient sample (n=723). As shown in Table 3, patients in both the PD and HD groups were further subdivided using the variables included in the study: age, gender, cardiac disease, HTN, diabetes, CVA, MI, dementia, depression, bipolar, cancer and lung disease. HD and PD patients did not significantly differ in terms of age at the time of dialysis initiation. In general, both groups of patients had a similar average age at the baseline (HD patients: 64.93, PD patients: 64.52, p= 0.784). Frequency of male and female patients in HD and PD modalities was also similar (males; HD patients: 63.5%, PD patients: 58.8%, p-value=0.361).

The comparison of baseline characteristics among the entire study cohort according to the type of modality revealed significant differences in cancer, diabetes and lung disease comorbidities. The prevalence of diabetes mellitus was significantly higher in PD patients than in HD patients (PD patients: 71.8%, HD patients: 62%, p = 0.045). In contrast, the number of HD patients with lung disease (PD patients: 16%, HD patients: 25%, p = 0.028) and cancer (PD patients: 22.1%, HD patients: 33.2%, p = 0.014) was significantly higher than the group of PD patients.

No significant differences existed between the two patients group (HD/PD) for HTN (HD patients: 88%, PD patients: 92%, p = 0.201), cardiac disease (HD patients: 57.3%, PD patients: 56.5%, p = 0.949), CVA (HD patients: 26.4%, PD patients: 30.5%, p = 0.287) and MI (HD patients: 27.7%, PD patients: 26%, p = 0.766).

HD and PD patients did not differ in respect of psychological indicators, such as bipolar (HD patients: 2.2%, PD patients: 3.8%, p = 0.443), and depression (HD patients: 29.2%, PD

patients: 30.5%, p = 0.848). There was a tendency for HD patients to suffer from dementia more frequently than PD patients, but these differences did not reach statistical significance (HD patients: 6.3%, PD patients: 2.3%, p = 0.114).

Figure 4 illustrates the modality distribution based on the defined five age categories. As expected from the overall distribution of HD and PD modalities, frequency of HD is higher in all age categories. Distribution of PD is roughly similar in all groups and only ranges from 16% to 22%. PD is most common in the group of 55-64 years old with 22% and least common in the group of 65-74%. Similarly, HD distribution is roughly similar in different age categories.
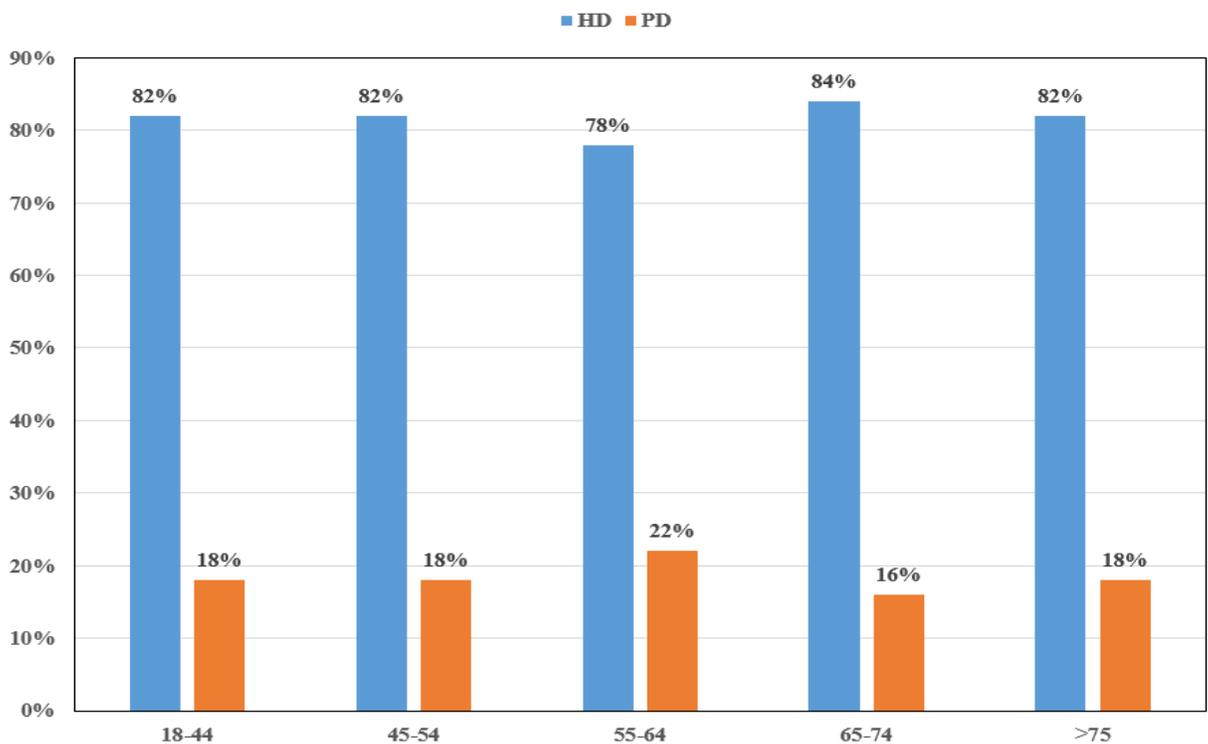
Figure 4. Modality distribution by age categories

Table 3. Baseline characteristics by dialysis modality

Characteristics	HD		PD		P-value
	Frequency	**Percentage**	**Frequency**	**Percentage**	
Age at dialysis initiation (Mean±SD)	64.93±14.8		64.52±15.34		0.784
Gender					
Male	376	63.5	77	58.8	0.361
Female	216	36.5	54	41.2	
Comorbidities					
Diabetes	367	62	94	71.8	0.045*
HTN	521	88	121	92.4	0.201
Cardiac disease	339	57.3	74	56.5	0.949
MI	164	27.7	34	26	0.766
CVA	156	26.4	40	30.5	0.387
Lung disease	151	25.5	21	16	0.028*
Cancer	199	33.6	29	22.1	0.014*
Mental health disorders					
Dementia	37	6.3	3	2.3	0.114
Bipolar	13	2.2	5	3.8	0.443
Depression	173	29.2	40	30.5	0.848

Asterisks denote difference between HD and PD; *significant at 0.05 level; **significant at 0.001 level

5.5. Kaplan-Meier (KM) survival curves

KM survival curves were generated to show the cumulative survival of the entire cohort during the study. Survival curves were stratified by important factors such as different age groups, gender and type of modality, to visualize the survival experience of dialysis patients in GRH. The KM survival curve estimating the overall survival of the incident chronic dialysis population during the study period is presented in Figure 5.

In Figure 5, the survival function has been graphed over the study follow-up time. There is a constant decrease in survival function during the study period as it started at 1 and went down in a decreasing direction to 0.27. A rise in the survival time of dialysis patients corresponds to a drop in their cumulative survival rate. The KM cumulative survival curve is surrounded by the 95% confidence intervals. The corresponding confidence intervals were relatively narrow, indicating the considerable reliability of the cumulative survival estimates.

The median survival time for all 723 patients was 39.8 months, which is the smallest survival time point for which the cumulative survival is less than or equal 50%. As shown in Figure 5, the 1-, 2-, 3-, 4- and 5-year survival rates for the incident chronic dialysis patients in GRH were estimated to be 0.80, 0.65, 0.54, 0.41 and 0.34, respectively.
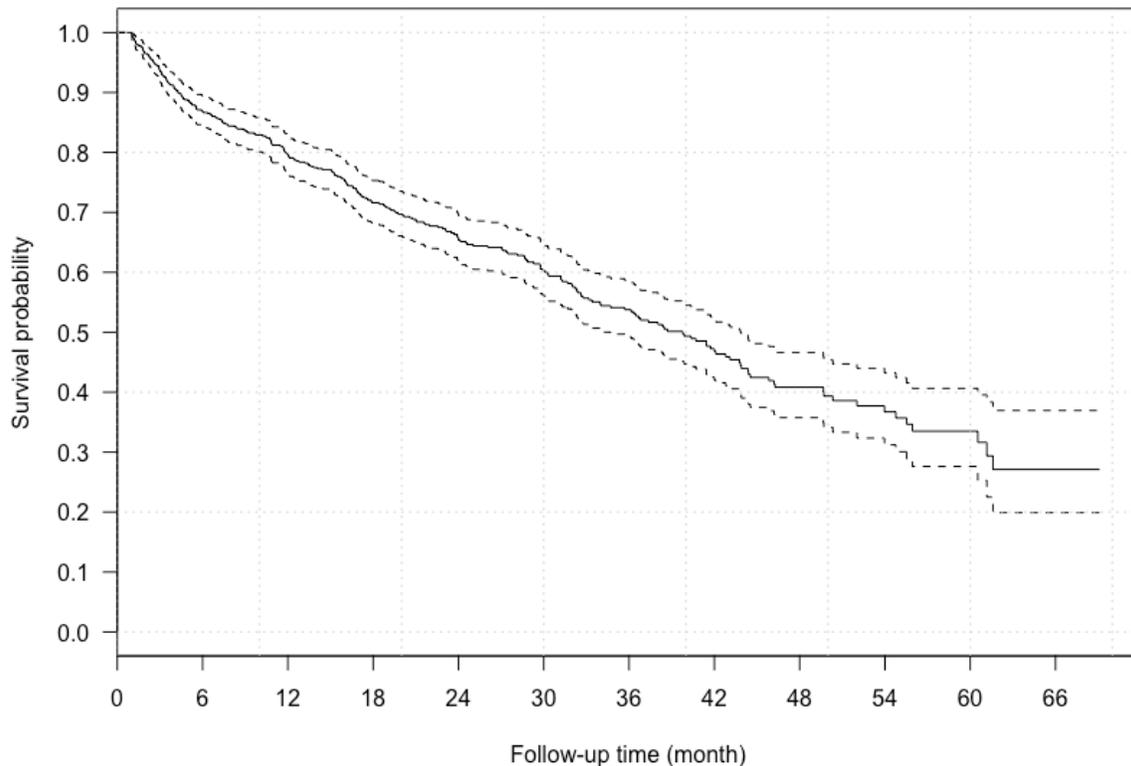
Figure 5. KM survival curve for all chronic dialysis patients (solid line) and the corresponding CI (dashed lines)

5.5.1. KM curves for different age categories

Figure 6 represents the KM curve for survival of the cohort, stratified by age categories. Corresponding age categorization was extracted from the CORR national renal registry (2017) in order to compare the survival rates for GRH. All the survival probabilities for all age groups start at a survival probability of 1 and step down to the other survival probabilities. These five age groups of patients appear to be quite different, as all of curves increasingly diverge over time.

As the graph demonstrates, the estimated survival probability for the youngest group of patients (18-44 years old) consistently lies above that of all other groups. This difference indicates that the youngest group of dialysis patients in GRH had a greater survival probability at all points of follow-up. The two youngest groups of patients (18-44 and 45-54 years old) are somewhat closer together in the first 42 months of the study duration. After this point, the two curves diverge slightly, then maintain a consistent distance apart until the study end.

For two groups of patients: 65-74, and older than 75 years old, Figure 6 shows a quick drop in survival probability in the 12 months of follow-up. During the first year of follow-up, these two groups experienced quite similar survival, but thereafter the survival probabilities start to diverge notably, a trend that continues until to the end of the study. The 65-74 group has a higher survival probability after the first twelve months of the study compared to the older group. Similar to the other groups, patients aged between 55 to 64 years old, had a constant decrease in survival probabilities during the study follow-up. The difference between this group and patients aged 65 to 74 years old is about the same over time except in the middle of the study period in which two curves converge a bit. Roughly, this difference remained the same until the end of the

study. In summary, as the number of months increases, the five age groups' KM survival curves appear to get farther apart, suggesting the beneficial impact of younger age over older groups.
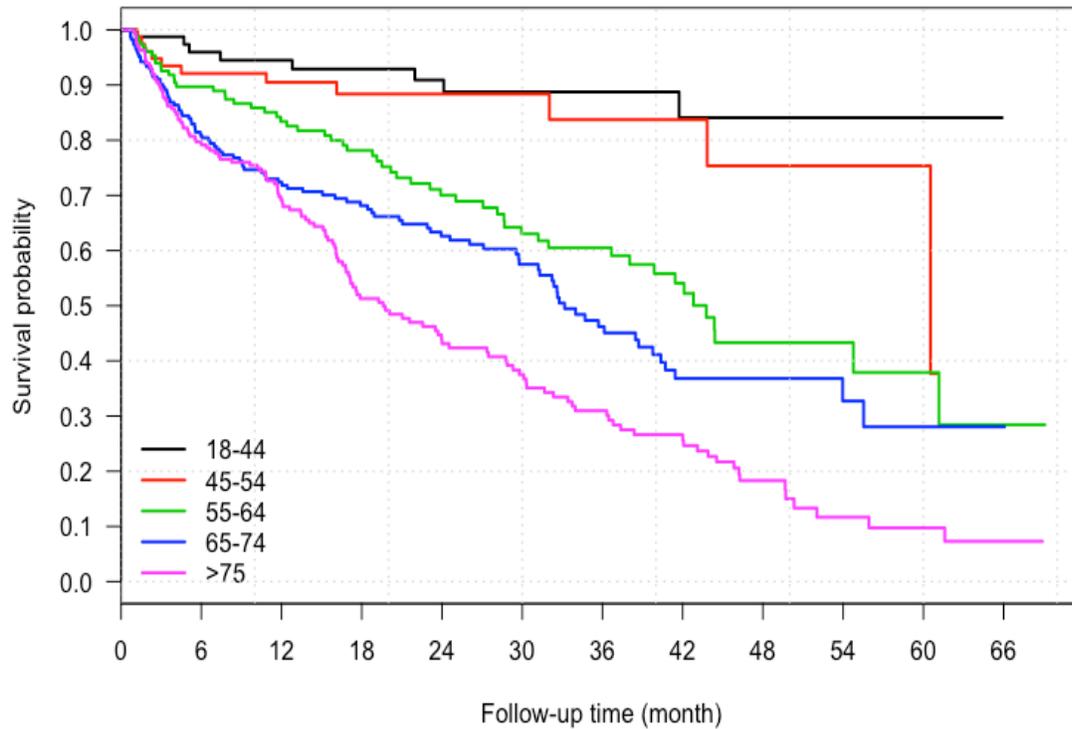
Figure 6. KM survival curve for chronic dialysis patients by age categories

In order to compare the survival of different groups, a log-rank test was conducted, providing a comparison of the overall survival experience of different age categories. Comparing the survival for the five different age categories reveals that the equality of survival functions had a p-value of less than 0.05, confirming that the survival probability of the five age categories significantly differed (Table 4 and Appendix F). Therefore, the null hypothesis that all five survival curves would be the same was rejected.

Table 4. Log-rank test for baseline age categories

	Number of patients	Number of deaths	5-year survival rate
Age			
18-44	80	8	0.85
45-54	78	11	0.77
55-64	156	56	0.38
65-74	227	98	0.29
>75	217	134	0.09
Log-rank test: p< 0.001			

5.5.2. KM curves for gender

Figure 7 is the KM curve for survival of the cohort stratified by gender. Survival probabilities appeared best for women during the first 48 months of the study. The KM curves initially separated with a higher survival probability for women until about 48 months of study follow-up. The survival probabilities of men and women converged as the KM survival curves crossed at 48 months of the follow-up time. The KM survival curves switched as men had a better survival probability until about 62 months of the study. To demonstrate, the one-year, 2-year, 3-year and 4-year survival rates for women were estimated as 0.81, 0.70, 0.59 and 0.41, respectively, while the rates for men were 0.79, 0.63, 0.51 and 0.41. Eventually again the trend switched as the 5-year survival rate was 0.29 for women and 0.36 for men.
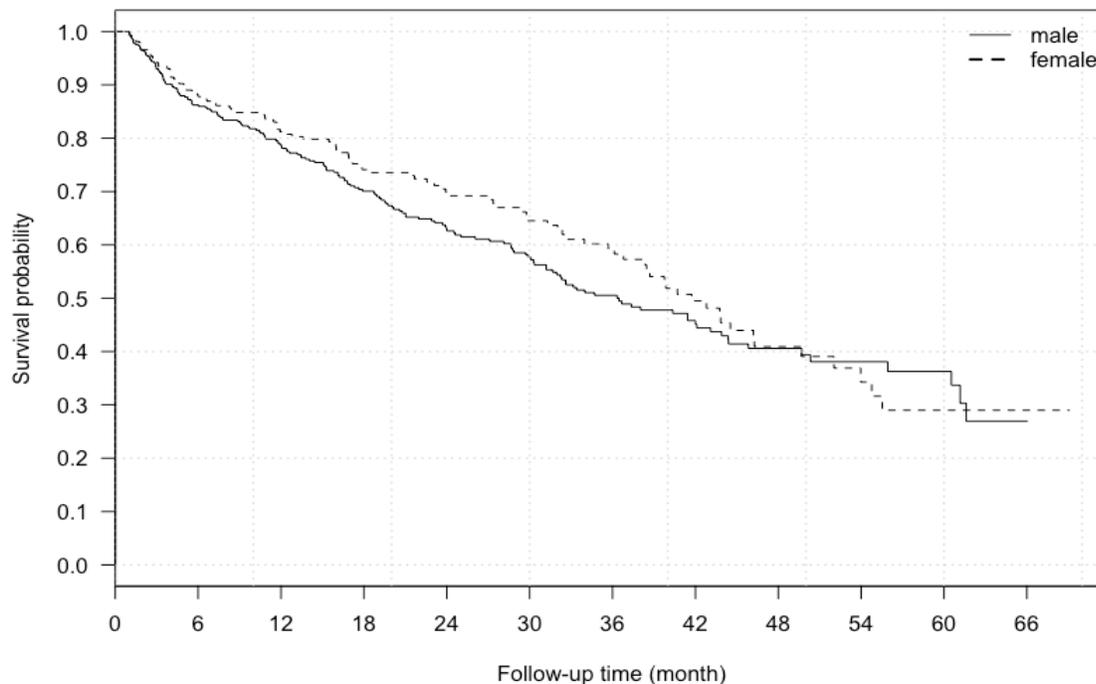
Figure 7. KM survival curve for chronic dialysis patients by gender

The quantified difference obtained from the log-rank statistical test suggests that there was no difference in the survival experience of men and women (p=0.263). Thus, the two survival curves (male and female) are not statistically different during the study period (Appendix G). Table 5 displays the log-rank test results for the male and female dialysis patients.

Table 5. Log-rank test for gender

	Number of patients	Number of deaths	5-year survival rate
Gender			
male	453	184	0.36
female	270	100	0.29
Log-rank test: p= 0.263			

5.5.3. KM curves for modality

Figure 8 displays the KM survival curves by baseline modality of the whole cohort. The median survival time for HD and PD patients was 38.7 and 39.8 months, respectively. As illustrated, there is a higher survival probability for PD patients early in follow-up. For example, one-year survival rate for PD patients equals 0.88 while this value is 0.78 for HD patients. Up to 18 months, the survival probability for PD is higher than that for HD, but thereafter the two survival curves are at about the same level. This graph indicates that up to 18 months the PD modality has better survival outcome than the HD but has about the same effect thereafter. To demonstrate, 2-year, 3-year, 4-year and 5-year survival for PD patients estimated as 0.65, 0.54, 0.42 and 0.28, while this rates were estimated as 0.65, 0.54, 0.41 and 0.34 for HD patients, respectively.
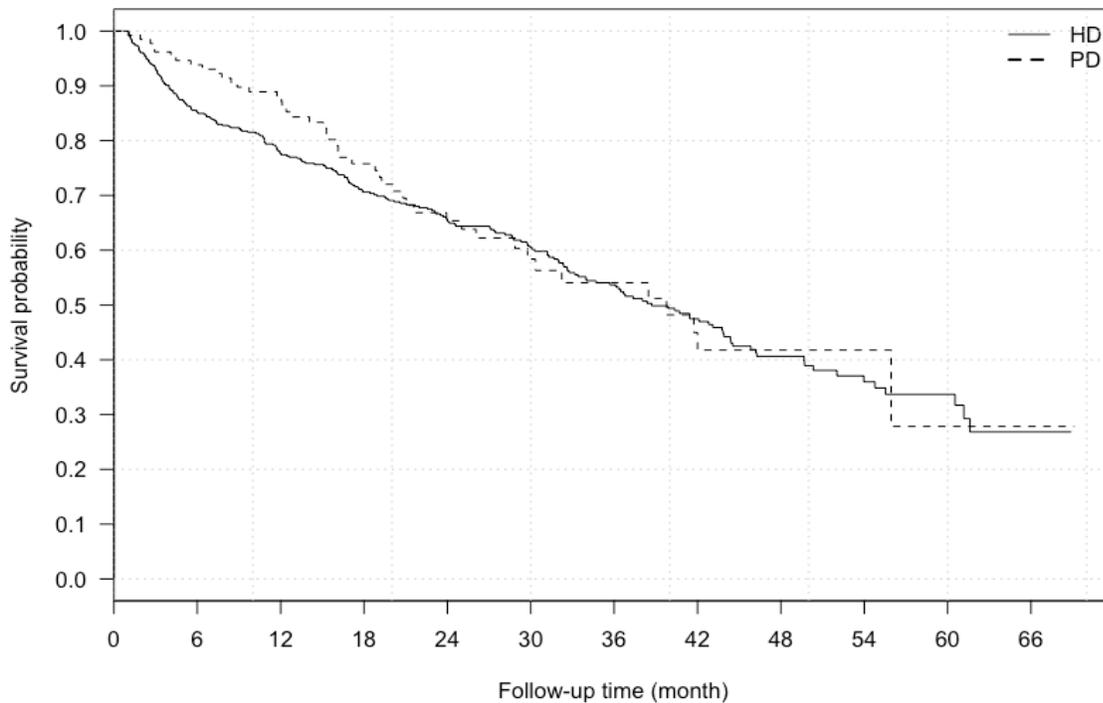
Figure 8. KM survival curve for chronic dialysis patients by type of modality

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The log-rank test for equality of survivor functions had a p-value of 0.464, confirming that the survival experience among two modalities was not significantly different (Appendix H). In fact, during the study follow-up time, type of dialysis modality (HD vs. PD) did not statistically differ despite the survival advantage of PD over HD during the early follow-up time (Table 6).

Table 6. Log-rank test for baseline modality

	Number of patients	Number of deaths	5-year survival rate
Modality			
HD	592	238	0.27
PD	131	46	0.28
Log-rank test, p= 0.464			

5.6. Multivariate analysis

The multivariate Cox proportional hazard model was calculated using a backward elimination variable selection procedure. Thus, in the first step the model was estimated with all the variables and the survival outcome. In succeeding iteration, non-significant variables (i.e., those that added least to the model) were eliminated in a stepwise order to achieve model parsimony. P-value > 0.2 and p-value > 0.1 were considered as the two exclusion criteria in the elimination procedure, resulting in models A and B, respectively. During the multivariate analysis, the age variable was considered as a confounder. The goal was to describe the effects of comorbidities, type of modality and gender on survival outcome adjusted for age.

During the backward elimination procedure, certain variables were retained and others dropped. In model A, variable elimination proceeded until all remaining variables in the model had p-values less than 0.2, resulting in a four variable model (Table 8 and Appendix I). As already described, at each subsequent step, the variable that added least to the model was

eliminated. In the first step, the initial model contained all thirteen variables: age, gender, modality, cardiac disease, HTN, CVA, MI, cancer, diabetes, lung disease, dementia, depression and bipolar disorder. In this step, depression was eliminated from the initial model, as it had the highest p-value, equal to 0.789. In the second step, CVA, with its p-value of 0.675, was eliminated. In step 3, caner showed the smallest contribution to the model, with a p-value of 0.669, so it was dropped. Subsequently, from steps four to five cardiac disease was dropped with the p-value of 0.519. Continuing the elimination procedure led to model A, where all variables (i.e., age, HTN, bipolar, lung disease) had p-values of less than 0.2 (Table 8).

The backward elimination continued with the cut-off of 0.1. In the two subsequent steps, bipolar and lung disease were eliminated with the p-values of 0.184 and 0.173, respectively. As a result, the final reduced model B contained only two variables: age and HTN. As illustrated in Table 7 and Appendix I, the backward elimination procedure with the cut-off of 0.1 took twelve steps in this study (counting Step 1 as the full model with all variables included, and Step 12 as the eventual reduced model). After step 12, no variable had a p-value above 0.1 (Table 7).

The majority of variables were not statistically significant enough to retain in either final model; thus, depression, CVA, cancer, cardiac disease, modality, diabetes, dementia, gender and MI were excluded. Type of modality was dropped from the backward procedure in the step 5 with the p-value of 0.433, indicating the non-significant impact of modality on survival (Table 7 and Appendix I).

Table 8, indicates the final two models with corresponding adjusted HR and p-values. Of the four retained variables in model A, bipolar and lung disease were insignificant predictors of survival, at the 0.05 significance threshold. Both bipolar and lung disease were positively

associated with mortality in this population without a statistical significance impact (bipolar: adjusted HR= 1.74, p= 0.184, lung disease: adjusted HR=1.21, p=0.154), (Table 8).

Both HTN and age remained significant throughout all steps of the backward elimination, and the estimated effects persisted (Appendix I and Table 7). In both final models A and B, hypertensive dialysis patients had a lower risk of mortality than the non-hypertensive group (model A: adjusted HR=0.62, p= 0.013, model B: adjusted HR=0.65, p= 0.023). Older patients had a higher risk of mortality in both model A and model B (model A: adjusted HR=1.05, p<0.001, model B: adjusted HR= 1.05, p<0.001).

Table 7. Backward elimination variable selection steps with the cutoff of 0.01

step	Included variables	Eliminated variable	Adjusted HR	95% CI	P-value
1	age, gender, modality, cardiac disease, HTN, CVA, MI, cancer, diabetes, lung disease, dementia, depression, bipolar	Depression	1.04	0.79-1.36	0.789
2	age, gender, modality, cardiac disease, HTN, CVA, MI, cancer, diabetes, lung disease, dementia, bipolar	CVA	0.94	0.72-1.24	0.675
3	age, gender, modality, cardiac disease, HTN, MI, cancer, diabetes, lung disease, dementia, bipolar	Cancer	0.95	0.74-1.22	0.669
4	age, gender, modality, cardiac disease, HTN, MI, diabetes, lung disease, dementia, bipolar	Cardiac disease	0.91	0.68- 1.21	0.519
5	age, gender, modality, HTN, MI, diabetes, lung disease, dementia, bipolar	Modality	0.88	0.64-1.21	0.433
6	age, gender, HTN, MI, diabetes, lung disease, dementia, bipolar	Diabetes	1.11	0.85-1.44	0.451
7	age, gender, HTN, MI, lung disease, dementia, bipolar	Dementia	0.80	0.51-1.27	0.343
8	age, gender, HTN, MI, lung disease, bipolar	Gender	0.87	0.68-1.11	0.258
9	age, HTN, MI, lung disease, bipolar	MI	0.87	0.67-1.12	0.278
10	age, HTN, lung disease, bipolar	Bipolar	1.74	0.77-3.94	0.184
11	age, HTN, lung disease	Lung disease	1.20	0.92-1.56	0.173
12	age, HTN	-	-	-	-

Table 8. Adjusted risk of mortality in two final models

Variable	Model A		Model B	
	Adjusted HR	P-value	Adjusted HR	P-value
Age	1.05	<0.001	1.05	<0.001
HTN	0.62	0.013	0.65	0.023
Bipolar	1.74	0.184	-	-
Lung disease	1.21	0.154	-	-

5.7. Verification of Cox proportionality assumption

The proportional assumption was tested both globally and individually on each of the retained variables in the final models. In both models, the proportionality assumption was satisfied as both the global p-value and the individual p-value for each variable were greater than 0.05. Therefore, the statistical inferences and prediction based upon the obtained models were reliable. Table 9 illustrates the results of proportionality assumption testing for models A and B.

Table 9. Proportionality assumption testing

Variables	Model A	Model B
	P-value	P-value
Age	0.266	0.194
HTN	0.812	0.621
Bipolar	0.782	-
Lung disease	0.142	-
Global	0.393	0.381

5.8. Model selection

Likelihood Ratio Test (LRT) is a statistical test used for the Goodness of Fit (GOF) comparison of two nested models. In the context of survival analysis, every Cox proportional hazard model can be compared with a null model (i.e., a model with no predictors, HR=1, β=0) to examine whether the obtained model fits the data or not. The LRT is based on the comparison of likelihoods of the two models which can be written as follows:

$$D = 2 \ln \left(\frac{L_A}{L_B} \right) = 2(\ln L_A - \ln L_B) \tag{9}$$

The D mathematically equals two times the difference in the logarithms of the likelihoods of two models. In this formula, L_A denotes the partial likelihood of the full model, and L_B equals the partial likelihood of the nested model. Given the null hypothesis that the two models fit the data equally well, the LRT statistics has an approximate chi-square distribution with the p_A-p_B degrees of freedom, where p_A and p_B denote the number of parameters in models A and B.

As mentioned, the backward selection procedure came up with model A (a full model with four covariates) and model B (a model nested within model A and having two covariates). LRT was used to test the null hypothesis if the null model is a preferred model in terms of providing satisfactory fit to the data or not. The p-values (less than 0.05) obtained from LRT revealed that both full and nested models fitted better than the null model with no predictors (Table 10).

Table 10. Model comparison

	D	P-value
Model A	110	<0.001
Model B	106.7	<0.001

The difference between the log likelihood statistics of the nested model and the log likelihood statistics of the full model was computed as: 2(1599.9-1598.3) = 3.2. The test statistics has a chi-square distribution with degrees of freedom equal to the difference in the number of covariates between the two models: 4-2 = 2, where 4 and 2 represent the number of covariates in model A and model B, respectively. Thus χ^2 with 2 degrees of freedom was compared with D. Since D = 3.2 is less than $\chi_2^2 = 5.99$, null hypothesis (i.e., H_0: model A = model B) is not rejected, and both models are statistically equivalent. In other words, models A and B provided adequate fit.

According to the principle of parsimony as the qualitative component of the model selection, it is worthwhile adopting model B because it is simpler than model A. Since both models provided adequate and similar fit, model B, as a more parsimonious model, was preferred.

Chapter 6: Discussion

6.1. Summary

The dialysis population represent one of the fastest-growing epidemics globally and in Canada, with a higher mortality rate than general population. In addition, this high rate of mortality, life expectancy among dialysis patients still remains significantly reduced due to the high prevalence of comorbid conditions such as Cardio Vascular Disease (CVD) and diabetes. As the epidemic of dialysis patients continues to emerge in Ontario, it is imperative to estimate the survival rate trends of dialysis centers and explore the survival outcome with different modalities. Patient survival has been considered an important index of overall adequacy of treatment in the majority of chronic illnesses such as cancer, and dialysis population (Charra et al., 1992). Accurate and comparable analysis of survival data is highly needed in different renal centers as some of the dialysis technologies may be having adverse outcomes while showing early promising results in some other centers.

In recent Canadian literature, only a few studies have compared the survival outcome of PD and HD patients (Yeates et al., 2012). Moreover, the exclusion of acute dialysis patients and inclusion of chronic dialysis patients have influenced the nature of the analytic sample. Previous studies lacked clear definition of chronic and acute dialysis, and some studies even failed to mention the exact description of the included patients in terms of chronic and acute. Multiple systems in GRH and existing sections were reviewed and screened by three individuals with clinical expertise and knowledge. Using KM survival curves in this study provided simple and quick insights at the survival experience of the cohort, and the Cox proportional hazard regression model yielded the association between variables and the survival outcome.

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The primary objectives of this study were to estimate the survival rate of incident chronic dialysis patients in GRH, compare the survival experience of patients receiving PD and HD, and finally identify significant predictors of mortality. In this regional community hospital, this research is the first attempt to estimate the survival rate of dialysis patients and investigate the survival outcome of HD and PD. There are three main points from this study which will be discussed separately: 1) Survival rate obtained from the analysis of patients treated with dialysis in GRH was comparable with other reported statistics, 2) During the study period, PD and HD had a similar survival outcome 3) Age and hypertension (HTN) had a significant impact on survival outcome. The results of this study may be used in counseling of patients requiring renal replacement therapy in GRH providing insight about their survival experience.

6.2.   Interpretation of key findings

6.2.1. Survival rate of dialysis patients in GRH

This study analyzed survival among 723 incident chronic dialysis patients in GRH during the study period of January 1th, 2012 to September 30th, 2017. The overall patients' survival rate obtained from this study, for the one-year, 2-year, 3-year, 4-year and 5-year were 0.80, 0.65, 0.54, 0.41 and 0.34, respectively. These survival rates in GRH were compared with recent statistics in Canada and USA such as CORR (Canadian Organ Replacement Registry)[1] and USRDS (United States Renal Data Systems)[2] national renal registries. The survival rates in this cohort were consistent with CORR and USRDS, illustrating high standards of provided care in

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[1] Canadian Organ Replacement Register (CORR) at the Canadian Institute for Health Information (CIHI), 2016, retrieved at: https://www.cihi.ca/en/canadian-organ-replacement-register-2016
[2] United States Renal Data Systems (USRDS), 2017, retrieved at: https://www.usrds.org/reference.aspx

the current renal program in GRH. In particular, 90-day survival of dialysis patients in GRH (0.94) were higher than survival of incident dialysis patients reported in CORR and USRDS reports with 0.91 and 0.92, respectively. One-year survival rate in GRH (0.80) was similar to the CORR and USRDS reports with the rate of 0.82 and 0.80, respectively. Survival outcome of dialysis patients in GRH compared to other registries highlights the clinical efficacy of the current renal program in this center.

6.2.2. Comparison of survival outcomes by modality

In an analysis of a contemporary cohort of 592 (81.8%) HD and 131 (18.1%) PD, patients in both modalities had a similar averaged age at the baseline (HD: 64.93, PD: 64.52, p=0.784). The prevalence of diabetes was significantly higher in PD patients than in HD patients (HD: 62%, PD:72%, p=0.045). On the other hand, cancer and lung disease were statistically more prevalent in the HD group (cancer: HD:33%, PD:22%, p=0.014, lung disease: HD:25%, PD:16%, p=0.028). Although in the preliminary analysis, unadjusted KM estimates showed a superior survival rate for PD compared to HD patients during the first 18 months after dialysis initiation, the overall survival outcomes of HD and PD patients were similar (log-rank test, p=0.464). Short-term survival rates of PD and HD patients during the first 18 months of dialysis initiation were 88% vs. 77% at three months, 88% vs. 77% at one year and 77% vs. 70% at 18 months, respectively. After 18 months of dialysis initiation, both PD and HD groups had similar survival rates (i.e., 65% at two years, 54% at three years and 28% at 68 months (endpoint of the study), respectively). The initial survival advantage of PD over HD may be explained by HD patients often having poor prognoses than PD patients. In fact, most severely ill patients requiring urgent treatment start renal replacement therapy with HD (Kim et al., 2014; Choi et al., 2013; Marshal

et al., 2015). Some other studies attribute this advantage to the younger distribution of PD patients (Wang et al, 2013); while this difference was not evident in this study. In our multivariate Cox proportional hazard model, type of modality was eliminated in the backward elimination procedure, adjusting for other variables with the p-value of 0.43 and hazard ratio of 0.88, illustrating the insignificance impact of modality on survival outcome during the study period.

The findings of the current study are in keeping with those of several studies, particularly Canadian ones, investigating the effects of type of modality on the survival of dialysis patients (Wong et al., 2017; Yeates et al., 2012; Fenton et al., 1997). A very recent retrospective cohort study by Wong et al., in 2017, analyzing 874 dialysis patients in seven regional dialysis centers in Ontario, yielded an insignificant effect of modality on survival and similar association of HD and PD with mortality during a nine-year study period (HR=1.09, 95% CI:0.82-1.45). Likewise, a number of large registry-based studies showed similar survival outcomes for both modalities (Yeates et al., 2012; Huang et al., 2008; Wang et al., 2013). The largest Canadian study, conducted by Yeates et al., in 2012, analyzing CORR data, revealed similar outcomes for both modalities during 13 years of follow-up. Based on Intention to Treat (ITT) analysis (i.e., attributing the hazard to the initial exposure regardless of any changes during the exposure (Marshal et al., 2015)) using the Cox proportional hazard model, the survival outcome remained the same for both HD and PD, with the average HR of 0.99 for the most-recent cohort (2001-2004) (Yeates et al., 2012). Similar to the KM survival rates obtained from GRH dialysis cohort by type of modality, CORR data showed an early survival advantage of PD over HD (one-year survival rate, HD:0.85, PD:0.9). Another similarly conducted study in Canada reported that the

use of CAPD/CCPD or HD is not associated with an increased risk of mortality (Fenton et al., 1997).

Survival analysis based on large-scale registries from other countries such as Taiwan have illustrated similar results. Again, using Cox proportional hazard and ITT analysis, Huang et. al., (2008) revealed that PD and HD patients experienced similar short-term and long-term survival outcome, after adjusting for demographic and clinical variables. In accordance with the current study's findings, PD and HD patients had similar long-term survival outcomes (Appendix D). No statistical difference was observed between these two groups (log-rank test, p=0.125). In total, the survival rates obtained from the Taiwan registry were higher than those estimated for GRH, except the one-year survival rates for PD patients which were similar (Taiwan:89%, GRH:88%). Another study in Taiwan, analyzing a subgroup from the same registry data, yielded similar overall survival among non-diabetic dialysis patients with a history of stroke (HR=1.2, 95% CI:0.96-1.5) (Wang et al., 2015).

In addition to large cohort studies, two small cohort studies with different study designs (retrospective vs. prospective) and inclusion strategies for patients (incident vs. prevalent) found similar survival outcome for the two dialysis techniques. Retrospective ITT analysis of incident dialysis patients in Hatzikosta General Hospital (HGH) in Greece by Andrikos et al. in 2008 exhibited no significant difference between HD and PD patients (55% vs. 50%; log-rank test, p=0.5), whereas the As-Treat analysis (AT, i.e., attributing the hazard to the last exposure (Marshal et al., 2015)) in this single center study illustrated significantly higher survival for PD patients HD ones (79% vs. 60%; log-rank test, p=0.04) (Andrikos et al., 2008). In comparison with the survival rate obtained in GRH, KM estimates for ITT approach revealed higher survival rates for patients in HGH center in Greece. The higher average age in incident dialyses patients

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at GRH (65 years old in GRH vs. 53 years old in HGH) may explain this difference. Analyzing the survival rates of prevalent dialysis patients recruited from three different dialysis centers in south-west Poland in four-year prospective study period showed that type of modality did not exert a significant impact on patient survival (log-rank test, p=0.83) (Madziarska et al., 2013).

As discussed, the majority of Canadian studies have highlighted the similarity of survival outcome among HD and PD patients (Yeates et al., 2012; Wong et al., 2017; Fenton et al., 1997); however, according to Sood et al., (2012) this finding might not be generalizable to all ethnic groups in Canada. Large-scale survival analysis of aboriginal patients, showed that PD modality was associated with higher risk of mortality (HR=1.36, p=0.001). According to studies in Taiwan (2013) and France (2011), patients with particular comorbid conditions had a poorer survival on PD compared to HD. Wang et al, in 2013, found that Taiwanese dialysis patients with pre-existing diseases, including diabetes or CVD, had inferior survival with PD compared to those receiving HD (HR=1.34, p<0.001). Similarly, Sens et al., in 2011 showed that incident dialysis patients with Congestive Heart Failure (CHF) commencing dialysis with PD in France experienced poorer survival rate than those with HD (HR=1.48, p<0.0001). The inclusion of specific ethnic groups of dialysis patients as well as those with specific type of comorbidities may explain this difference, with other studies indicating similar outcome for both modalities.

A few other investigators have reported superior outcomes for PD over HD, particularly in younger group of patients (Marshal et al., 2015; Choi et al., 2013). A nationwide prospective Korean study in 2013 by Choi et al., exhibited significantly improved survival outcomes for PD patients (HR=0.63, 95% CI: 0.36-1.08). Comparison survival analysis of Australian and New Zealand dialysis populations in a time-dependent approach also noted this observation, as the survival of PD patients was greater than that of HD patients during the study follow-up (Marshal

et al., 2015). Generally, authors tend to speculate that the superiority of PD over HD might be due to the possible improved patient selection for PD and the lesser burden of comorbidities in this group over time (Choi et al., 2013; Marshal et al., 2015).

Retrospective study design, inclusion of incident dialysis patients with a specific time-lag, similar geographic location (except in the study by Andrikos et al., in 2008 conducted in Greece), and an ITT analysis approach were the characteristics in common among the current study and the studies by Wong et al., (2017), Yeates et al., (2012) and Andrikos et al., (2008). The last two studies applied both ITT and AT analysis approaches to investigate any possible statistical differences in the modality comparison. It is worthwhile to mention that the results from ITT analysis in both studies were similar to our study's findings. Despite the use of ITT analysis in two other studies by Sood et al., (2012) in Canada, and Choi et al., in Korea, (2013), the survival outcomes of HD and PD were diverged. A possible explanation for this variation may be the large sample size and inclusion of aboriginal patients in the study by Sood et al., (2012) and the prospective study design, small cohort size and different geographic location (i.e., Korea) in the study by Choi et al., (2013). Similar findings from Canadian studies, including ours, highlight the equivalency of both modalities in terms of survival outcome and therefore can be offered equivalently to incident dialysis patients.

6.2.3. Significant predictors of survival outcome

From the current analysis, we were able to identify significant variables associated with survival outcome in GRH chronic dialysis patient population. During all the steps of backward elimination procedure adjusting for age, HTN remained significant with the exclusion cut-offs of greater than 0.1 and 0.2 p-values. Multivariate Cox proportional hazard regression has

highlighted the reverse association of HTN and survival outcome in this cohort. The results suggest that the presence of HTN as a coexisting comorbidity at the time of dialysis initiation was strongly associated with improved survival outcome (Model A: HR=0.62, p= 0.013, Model B: HR=0 0.65, p= 0.023). According to model A, non-hypertensive dialysis patients at the baseline had a higher risk of death compared to hypertensive dialysis patients, with the adjusted HR of 0.65.

The majority of the included chronic dialysis patients were hypertensive at the time of dialysis initiation (88.8% of the whole cohort). The distribution of hypertensive patients was similar for both types of modalities (HD: 88%, PD: 92%, p=0.201). Consequently, this finding may be generalizable to both groups of dialysis patients. Supplementary analyses to determine whether there was a statistical difference in the group of hypertensive and non-hypertensive patients did not reveal any significant differences in the groups of hypertensive and non-hypertensive patients in terms of age (Table 2).

The finding of this study regarding HTN was supported by several epidemiological studies confirming the U-shaped relationship between mortality and HTN. Some of the existing studies refer to this phenomenon as "reverse epidemiology", indicating a paradoxical association between mortality and the effect of hypertension in dialysis patients. Kalantar-zadeh et al., (2005) reported the survival advantages of high blood pressure among dialysis patients. Similarly, survival analysis of HD patients enrolled in the DOPPS registry demonstrated that a history of hypertension was significantly associated with decreased risk of mortality in both univariate (HR=0.85, p<0.0001) and multivariate analysis (HR=0.74, p<0.0001) (Goodkin et al., 2003). The findings of the DOPPS study coincided with the association obtained in this study, and with Hwang et al.,'s investigation of various comorbidities' impacts on the survival outcome

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of HD patients in Taiwan, which also illustrated a reverse association of hypertension presence at the time of commencing dialysis (HR=0.79, CI:0.7-0.89) (Hwang et al., 2010). Furthermore, in a similar study conducted in Taiwan in a duration of 10 year follow-up, HTN was a statistically significant protective variable for mortality (HR=0.84, p<0.001) (Wang et al., 2013). Comparing survival experience of HD and PD patients with and without history of CVD in this study, highlighted the history of HTN as an independently protective effect on survival outcome (Wang et al., 2013).

As mentioned, the linear relationship between HTN and increasing cardiovascular, cerebrovascular events and mortality in the general population is indisputable (Lim et al., 2012; Perkovic et al., 2007). In the same way, in the dialysis population, some studies have showed the increased risk of mortality in the presence the of HTN. In contrast to the reverse epidemiology of hypertension, survival analysis of Indonesian hemodialysis patients by Purnama et al. (2015), suggested increased risk of mortality in hypertensive patients with the hazard ratio of 1.04. In line with these reports that contradict our findings, Lucas et al. (2003), found uncontrolled HTN to be an independent risk factor for both all-cause mortality (HR=1.79, p=0.01) and cardiovascular mortality (HR=2.93, p=0.00). Uncontrolled HTN was defined as blood pressure greater than 140/90 mm Hg, whereas this threshold was above 150/85 mm Hg in the study by Agarwal et al., (2003). Two cohort studies in Tassin, France, reported the independent association of HTN and increased risk of mortality in HD patients (Charra et al., 1992). According to the literature, however, some studies have failed to show any significant association between existence of HTN as a comorbid condition and survival in dialysis patients (Andrikos et al., 2008; Yang et al., 2015; Huang et al., 2008; Wang et al., 2016).

As discussed, the current finding of this study indicated that the presence of hypertension as a comorbid condition at the time of initiating dialysis showed a protective effect on survival outcome. There are several possible explanations for this finding in the literature, for instance, discrete (binary) categorization of hypertension at the baseline as (yes or no) instead of using blood pressure as a continuous variable (SBP, DBP) (Agarwal, 2005; Hwang et al., 2012). Binary categorization of hypertension indeed did not reveal how severe it was at the baseline. This categorization, due to insufficient information on blood pressure measurements, and duration of antihypertensive medication use or any relevant treatment at the baseline, could have resulted in reporting normotensive or well controlled hypertension patients as hypertensive. To demonstrate, there is a possibility that some patients who were being treated with antihypertensive medication therapy for a long time and who had already become normotensive were categorized as hypertensive (Hwang et al., 2012). Based on the review conducted by Agarwal in 2005, the use of antihypertensive medication treatment is associated with improved survival regardless of how well the high blood pressure is under control. Emerging evidence on impact of antihypertensive medications on dialysis patients' survival also provides independent cardio protection in hypertensive patients. For example, use of ACE[1] and ARB[2]'s antihypertensive medications help decreasing glomerular pressure and protect the nephron.

A number of large cohort studies confirmed elevated risk of mortality for dialysis hypotensive patients and did not report a higher risk of mortality for those with increased level of blood pressure, which suggests the U-shaped relationship (morality and hypertension) (Agarwal, 2005). Clinically, hypotension is an indicator for significant comorbidities such as heart failure

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[1] Angiotensin Converting Enzyme
[2] Angiotensin Receptor Blockers

or ischemic cardiomyopathy (Molnar et al., 2012). Several studies confirmed that hypotension had a stronger signal for mortality that HTN in dialysis patients. Kalantar-zadeh et al., (2005), illustrated that a range of normal to low blood pressure is associated with poor clinical outcome among dialysis patients. Likewise, both time varying and discrete categorization of hypertension in a study by Li z et al., (2006) showed that risk of mortality tends to be greater at normal and low levels of blood pressure. In the current study, there is a possibility that hypotensive patients were reported and categorized as non-hypertensive, reflecting poor survival outcome.

The other possible explanation is uncertainty about the definition of HTN presence at dialysis initiation. It was also not clear what specific threshold was considered for presence of HTN. Some of the studies defined HTN as taking current antihypertensive medication or self-report of having a previous clinical diagnosis (DOPPS) while others identified a specific threshold for normal blood pressure (Tong et al., 2016). Tong J et al., defined HTN as if the patient was taking antihypertensive medication or had a blood pressure of greater than 140/90 mm Hg in two different occasions while the study by Lacus identified uncontrolled hypertension with a blood pressure greater than 140/90 mm Hg. In another study by Agarwal et al., HTN was defined as an average pre-dialysis blood pressure greater than 150/85 mm Hg (Agarwal et al., 2003). In spite of widely used of these thresholds in this context, some reports show routine pre-dialytic blood pressure recordings are not sufficient to accurately diagnose HTN. High variability in session-to-session blood pressure may explain the poor diagnostic accuracy of pre-dialysis blood pressure recordings (Georgianos & Agarwal, 2016).

Finally, there is possibility that non-hypertensive patients had other preexisting diseases or clinical abnormalities that were not captured in this study. In this case, there is a possibility that presence of HTN as a risk factor was confounded by unmeasured parameters contributed to

the poor survival outcome. Adjustments for laboratory values and other comorbidities in other studies may explain the differences in findings between this study and others.

6.2.4. Non-significant predictors

The presence of comorbidities (i.e., other than HTN) and mental health disorders did not have a significant impact on the survival outcome in the current study. All the comorbidities except two of them which were lung disease and HTN and all mental health disorders except bipolar were dropped during the backward elimination procedure. In the model A with the exclusion cut-off of p-value>0.2, HTN and age were the only significant variables while lung disease and bipolar were two non-significant variables. In model B with the exclusion cut-off of p-value>0.01, HTN and age remained as the only significant variables without non-significant variables in the model. Other than comorbidities and mental health disorders, gender also did not confer a significant effect on survival outcome which is highly supported by several studies (Yang et al., 2015; Kim et al., 2014; Serafinceanu et al., 2014; Choi et al., 2013; Sens et al., 2011; Yeates et al., 2012; Shabankhani et al., 2016; Sood et al., 2012). For example, a survival analysis of 500 HD patients in Mazandaran, Iran using three hospitals data during a 6-year study period demonstrated non-significant effect of gender on mortality (Shabankhani et al., 2016). Published results from two large cohort studies in Canada by Yeates et al., (2012) and Sood et al., (2012) revealed that gender did not influence survival. Another large-scale study in France by Sens et al., (2011) also confirmed the non-significant of this association. In accordance with these findings, two prospective studies compiling data from different hospitals in Korea and Poland, respectively with small cohort size also highlighted this association (Choi et al., 2013; Madziarsk et al., 2013). It is worthwhile to mention that direction of the association (i.e.,

improved survival for females) in the majority of these studies were similar to the current study (Shabankhani et al., 2016; Choi et al., 2013; Madziarsk et al., 2013).

Cancer: In this study history of cancer at the baseline did not appear to affect the outcome significantly as it was also found in other studies. A nationwide prospective cohort study in Korea founded no significant effect of cancer on the survival outcome (Choi et al., 2013). A retrospective study by Béchade et al. (2017), also did not reveal any association between history of cancer at the baseline and survival outcome among incident dialysis population. Similarly, survival analysis of aboriginal and Caucasian Canadian dialysis patients receiving HD and PD therapies, identified history of cancer as a non-significant predictor of mortality (Sood et al., 2012). Another study in Taiwan, demonstrated the non-significant impact of cancer as a comorbid condition at the baseline on survival of PD and HD patients with prior stroke (Wang et al., 2016). Higher prevalence of cancer in HD group of patient was consistent with many studies in this context such as those conducted by Sood et al., (2012) Wang et al., (2013, 2016) and Choi et al., (2012).

Diabetes: Presence of diabetes at the dialysis initiation adjusted for age, also did not confer a significant influence on survival outcome. Multiple studies have found non-significant impact of diabetes on survival. In a retrospective study by Koch et al., (2006) analyzing survival data in a single-center in Germany, diabetes proved not to be an independent predictor of mortality. Another prospective registry-based, observational study in Scotland revealed that presence of diabetes did not influence the 2-year survival of patients initiating dialysis (Metcalfe et al., 2003). A French study analyzing survival experience of PD and HD patients with CHF also demonstrated non-significant impact of history of both types of diabetes (i.e., type 1 and type 2) on survival outcome (Sens et al., 2011).

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Lung disease: Although lung disease remained in the model A during the backward elimination, similar to other comorbidities did not affect survival outcome. Consistent with other studies' findings, a very recent multicenter prospective cohort study in Korea by Park et al., (2018) demonstrated non-significant impact of chronic lung disease history on survival using Cox proportional hazard model. Direction of the obtained association in this study was similar to our study as well. Similar to the study by Park et al., (2018) mortality comparison between HD and PD patients in France revealed that chronic lung disease did not exert significant effect (Sens et al., 2011).

Cardiac disease, MI and CVA: On the age-adjusted multivariate analysis, along with other comorbidities except HTN, presence of MI, cardiac disease and CVA did not exert a significant impact on survival which is also supported by some of the studies such as a study by Xia et al., (2017). In this observational study incident adult PD patients were enrolled to build a predictive model using Lasso Cox regression model. Presence of MI was not a significant predictor for mortality in this population (Xia et al., 2017). In multiple studies CAD as the most common type of cardiac disease showed nonsignificant effect of the survival outcome. In an observational study survival analysis of Australia and New Zealand and Transplant Registry (ANZDATA) data, identified CAD as a non-significant predictor of all-cause mortality during a 5-year study period (Lawton et al., 2015). Similarly, a retrospective small cohort study in Greece, found CAD as an insignificant variable in a survival comparison of incident HD and PD patients (Andrikos et al., 2008). Despite the consistency of these findings, some of the studies pointed out CAD and MI as important mortality risk factors in dialysis populations (Wang et al., 2013; Tong et al., 2016; Lee et al., 2014 & Hocher et al., 2008).

Another statistically insignificant relationship in the current study was the impact of CVA on survival. In spite of CVA prevalence among chronic dialysis patients, there are a number of studies in the literature supporting this finding. In an observational prospective study investigating the potential associations of several risk factors with early and overall mortality in a single-center dialysis cohort in the UK, presence of CVA was not significantly associated with mortality (Cherukuri & Bhandari, 2009). There are some possible explanations for the existing difference in this context such as merging different heart failure problems and risk factors into one category in other studies (e.g., combining MI, CAD and CVA into one category), variability in study designs, statistical techniques, follow-up duration, sample size, demographic characteristics, etc.

Mental health disorders: Many authors have discussed the importance of assessing psychiatric disorders among candidates for initiating dialysis; however, investigations of the associations between these groups of comorbidities and survival outcome among incident dialysis population revealed different results (Rakowsk et al., 2006; Rosenthal et al., 2012). Similar to our findings, early studies using valid measures of depression provided preliminary evidence that all-cause mortality was not significantly affected by the presence of depression. For instance, survival analysis of 97 patients undergoing renal replacement therapy such as HHD and PD, indicated presence of depressive symptoms did not influence the survival outcome (Devins et al., 1990). A prospective, longitudinal, multicenter study of urban HD patients, also demonstrated that depression was not a mortality predictor (Kimmel et al., 1998).

Subsequent studies also did not find any association between baseline depression symptoms and increased risk of mortality among incident dialysis patients (Kimmel et al., 2000; Boulware et al., 2006). Extensive evaluation of depression symptoms among 323 chronic HD

patients revealed that impact of depression on survival outcome was attenuated when adjusted for comorbidities, suggesting presence of a complex relationship between depression and clinical characteristics (Fan et al., 2014). There are some studies revealing significant impact of mental health disorders such as a study by Goodkin et al., (2003), examining all psychiatric disorders at the same time similar to our study. Survival analysis of HD patients across different regions in DOPPS registry as a prospective, observational cohort also demonstrated significant impact of mental health disorders such as dementia, depression and bipolar on survival (Goodkin et al., 2003). In DOPPS registry, history of dementia along with history of Parkinson disease was categorized as neurologic disease comorbidity condition. Both depression and bipolar along with a history of alcohol and schizophrenia were categorized as psychiatric disorders.

Different study designs, large registries vs. single center, various criteria for evaluating mental health disorders, different categorization and combining various disorders into one category may explain different results. Moreover, there is a scarcity of studies assessing the impact of mental health disorders, particularly dementia and bipolar. The low prevalence of mental health disorders variables in this study suggests that mental health status might be underreported in the GRH renal systems. It is therefore likely that patients who were identified as not having mental disorders would not have been assessed or even asked for such problems. Such possible underreporting or misclassification generally would bias obtained associations toward lack of statistical significance (Gordis, 2013).

6.3. Strengths, limitations and future direction

6.3.1. Strengths

Local hospital-based renal data analysis conducted in this research is an important and timely contribution to existing dialysis outcomes in Canada. This survival analysis using GRH renal data is a first attempt estimating survival rates among chronic dialysis patients in the Waterloo region. The results from this study can help to provide relevant guidance for the individualization strategies for chronic dialysis patients receiving care at GRH. Although there have been a number of studies in various geographic locations on survival outcome, they have largely neglected various important comorbidities. No contemporary studies on the survival analysis of incident chronic dialysis patients in Canada have included a wide range of comorbidities and mental health disorders in their models in the current era. However, obtaining survival outcomes and the relevant impact of comorbidities, can provide some relevant insights to nephrologists and clinical teams. Using these insights on similar survival outcome of HD and PD modalities will help enhance long-term and short-term prognoses, particularly for patients in GRH or for those who are similar to this cohort in terms of both ethnic and medico-social aspects.

Information from this analysis will contribute to building and developing patient profiles, resulting in better outcome prediction for new dialysis patients. Model validation has demonstrated significant prognostic information gained by applying the two models. The Cox proportional hazard model may eventually evolve into 'counseling-decision tool' to facilitate decision making regarding modality choices at dialysis initiation.

Previous studies have not always accounted for incident versus prevalent and acute versus chronic. The 30-day lag in differentiate between chronic and acute dialysis patients was considered for evaluating survival in this cohort. Survival rates obtained from this study clearly indicate the current status of dialysis therapy among incident chronic patients receiving dialysis in GRH. Owing to the robust data collection and relatively long follow-up (up to 68 months) period of this study, the results can be compared with other regional or population-based cohorts and single center studies in Canada.

6.3.2. Limitations

As with other retrospective observational studies, this study also has limitations inherent to such a study design. In view of the retrospective design of the current study, we were able to describe corresponding associations between predictors and survival outcome rather than establishing causality. In fact, such an observational retrospective study can only provide information on the effectiveness of modalities rather than any causality between modality and mortality (Yang et al., 2015). Ideally prospective and case control study designs would be the most suitable for comparing the survival outcomes between different dialysis modalities. Non-random individual selection and assignment of patients to dialysis modality did not allow us to adjust for potential biases. Even though in some cases it is not possible to randomly assign patients to different modalities, appropriate statistical methods, particularly those using time-varying covariates, will allow for more robust comparison of survival outcome in different modalities. For instance, time-varying measurements of variables such as HTN would help to better understand how well dialysis patients may respond to dialysis therapy. Therefore, cross-

sectional analysis of variables in this study, instead of multiple time dependent values is a major limitation of this study.

Another limitation of this study is lack of adjustment for some of the important variables, due to either the retrospective study design, data quality issues or insufficient information such as laboratory values, nutritional status, smoking, ethnicity and quality of life. Any of these factors could potentially confound the association of predictors and survival outcome and therefore could result in biased estimates in the study. Since information extracted from Nephrocare and Nephroport was mainly collected for clinical records, it may not contain variables important to addressing the research questions.

Despite adjusting for various comorbidities and mental disorders, binary categorization (analysis) did not necessarily account for the severity level of those disease at the baseline in this analysis. Incomplete information on comorbidities such as duration of medication treatment and the stage of the diseases in this cohort could have influenced the results. Hence, it is likely that patients with different levels of disease severity and duration were categorized under the same group.

Although hospital-based data of the current research provides enough of eligible patients for the analysis, the study findings are prone to confounding by unmeasured variables such as socio-demographic factors and known confounders in this context, like modality switches. It is worth mentioning that studies that accounted for modality switches did not find significant differences in their survival outcomes (Perl et al., 2011).

Even though relevant insights have been extracted from this study, these findings may not be generalizable to other cohorts due to some reasons such as the retrospective observational design of the study, and differences in clinical practices and patients' characteristics across different

centers and countries. The data used for this study was extracted from a single center and may not reflect the survival outcome in other study sites. Moreover, the results of this study were not confirmed by applying propensity score matching to control confounding factors and overcome the limitation of non-random allocation of patients to HD and PD (Choi et al., 2013). Finally, treating all censoring as independent of survival outcome is a potential limitation of this study and might have led to biased results.

6.3.3. Implications and future directions

Based on the findings and limitations of this study, some new research questions have been raised that could lead to topics for future studies. For instance, detailed analysis of survival outcome by initiation year could be performed to further evaluate the survival trend in GRH. Future studies accounting for modality switches and time-variant measurements of modalities are needed to provided robust evidence on the effectiveness of dialysis options, which could eventually lead to better choices among alternatives.

A prospective, case-control study would allow assessment of important variables such as quality of life, smoking status and race as important predictors. Adjusting the Cox model for variables such as BMI and critical laboratory variables would better represent the modality comparison and increase the credibility of the results. For better prognostics, a clinical and laboratory time-varying covariate approach capturing the dynamic of the indicators over time is suggested.

It is often argued that backward elimination variable selection is more efficient than forward since the importance of the variable is not assessed in the context of other variables

(Guyon et al., 2003). Although in this study backward elimination was found to be preferable to forward, other techniques such as lasso -a robust technique- is strongly suggested.

Also the use of propensity score matching method in future studies is recommended to adequately control for potential confounding factors and so overcome the non-randomized allocation of dialysis patients to different modalities (Choi et al., 2013). Further large-scale cohort studies in Canada with sophisticated study designs are required to confirm the similar outcome of PD and HD modalities.

6.4. Conclusions

Cox proportional hazard model and KM survival curves were developed to identify the association of different variables with survival outcome and to estimate the survival experience of dialysis patients over a period of 5 years. This study showed acceptable survival rates for chronic dialysis patients in GRH, a significant protective impact of HTN, non-significant impact of modality on survival outcome and similar outcome for both HD and PD techniques during the study follow-up. Although the initial advantage for PD was greater than that of HD, long-term results were equivalent for both modalities in GRH. Following the findings of this study, PD and HD can be equally offered to all incident dialysis patients. As a result, more focus should go towards the quality of life and goals of therapy at the stage of care planning with patients.

References

Abecassis, M., Bartlett, S. T., Collins, A. J., Davis, C. L., Delmonico, F. L., Friedewald, J. J., ... & Merion, R. M. (2008). Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI™) conference. *Clinical Journal of the American Society of Nephrology*, *3*(2), 471-480.

Ajiro, J., Alchi, B., Narita, I., Omori, K., Kondo, D., Sakatsume, M., ... & Gejyo, F. (2007). Mortality predictors after 10 years of dialysis: a prospective study of Japanese hemodialysis patients. *Clinical Journal of the American Society of Nephrology*, *2*(4), 653-660.

Ahmad, S. (2009). *Manual of clinical dialysis*. Springer Science & Business Media.

Ahmad, Z., & Shahzad, I. (2015). Survival Analysis of Dialysis Patients in Selected Hospitals of Lahore City. *Journal of Ayub Medical College Abbottabad*, *27*(1), 205-7.

Allison, P. D. (2010). *Survival analysis using SAS: a practical guide*. Sas Institute.

Andrikos, E., Tseke, P., Balafa, O., & Pappas, M. (2008). Five-year survival in comparable HD and PD patients: One center's experience. *The International journal of artificial organs*, *31*(8), 737-741.

Arogundade, F. A., Sanusi, A. A., Hassan, M. O., & Akinsola, A. (2011). The pattern, clinical characteristics and outcome of ESRD in Ile-Ife, Nigeria: Is there a change in trend?. *African health sciences*, *11*(4), 594-601.

Badve, S. V., Paul, S. K., Klein, K., Clayton, P. A., Hawley, C. M., Brown, F. G., ... & Johnson, D. W. (2014). The association between body mass index and mortality in incident dialysis patients. *PloS one*, *9*(12), e114897.

Béchade, C., Dejardin, O., Bara, S., Bouvier, V., Guizard, A. V., De Mil, R., ... & Lobbedez, T. (2017). Survival of patients with cancer starting chronic dialysis: data from kidney and cancer registries in Lower Normandy. *Nephrology*.

Beddhu, S., Bruns, F. J., Saul, M., Seddon, P., & Zeidel, M. L. (2000). A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *The American journal of medicine*, *108*(8), 609-613.

Besarab, A., Bolton, W. K., Browne, J. K., Egrie, J. C., Nissenson, A. R., Okamoto, D. M., ... & Goodkin, D. A. (1998). The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *New England Journal of Medicine*, *339*(9), 584-590.

Bethesda M. US Renal Data System, USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States (2011). *National Institute of Diabetes and Digestive and Kidney Diseases*. 2011;10.

Boulware, L. E., Liu, Y., Fink, N. E., Coresh, J., Ford, D. E., Klag, M. J., & Powe, N. R. (2006). Temporal relation among depression symptoms, cardiovascular disease events, and mortality in end-stage renal disease: contribution of reverse causality. *Clinical Journal of the American Society of Nephrology*, *1*(3), 496-504.

Bradbury, B. D., Fissell, R. B., Albert, J. M., Anthony, M. S., Critchlow, C. W., Pisoni, R. L., ... & Gillespie, B. W. (2007). Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clinical Journal of the American Society of Nephrology*, *2*(1), 89-99.

Bruce, N., Pope, D., & Stanistreet, D. (2008). Quantitative methods for health research: a practical interactive guide to epidemiology and statistics. *John Wiley & Sons*.

Charra, B., Calemard, E., Ruffet, M., Chazot, C., Terrat, J. C., Vanel, T., & Laurent, G. (1992). Survival as an index of adequacy of dialysis. *Kidney international*, *41*(5), 1286-1291.

Cherukuri, A., & Bhandari, S. (2009). Analysis of risk factors for mortality of incident patients commencing dialysis in East Yorkshire, UK. *QJM: An International Journal of Medicine*, *103*(1), 41-48.

Chien, C. C., Sun, Y. M., Wang, J. J., Chu, C. C., Lu, C. L., Wang, S. F., ... & Chen, H. A. (2013). Increased risk of mortality among haemodialysis patients with or without prior stroke: a nationwide population-based study in Taiwan. *The Indian Journal of Medical Research*, *138*(2), 232.

Chilcot, J., Davenport, A., Wellsted, D., Firth, J., & Farrington, K. (2010). An association between depressive symptoms and survival in incident dialysis patients. *Nephrology Dialysis Transplantation*, *26*(5), 1628-1634.

Choi, J. Y., Jang, H. M., Park, J., Kim, Y. S., Kang, S. W., Yang, C. W., ... & Kim, Y. L. (2013). Survival advantage of peritoneal dialysis relative to hemodialysis in the early period of incident dialysis patients: a nationwide prospective propensity-matched study in Korea. *PLoS One*, *8*(12), e84257.

Chou, C. L., & Fang, T. C. (2013). Coronary artery disease in dialysis patients: What is the optimal therapy?. *Tzu Chi Medical Journal*, *25*(2), 82-85.

Clark, L. E., & Khan, I. (2010). Outcomes in CKD: what we know and what we need to know. *Nephron Clinical Practice*, *114*(2), c95-c103.

Collett, D. (2015). *Modelling survival data in medical research*. CRC press.

Collins AJ, F. (2012). United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end stage renal disease in the United States. *AmJKidneyDis*, *59*(1Suppl1), A7.

Collins, A. J., Kasiske, B., Herzog, C., Chavers, B., Foley, R., Gilbertson, D., ... & Matas, A. (2005). Excerpts from the United States Renal Data System 2004 annual data report: atlas of end-stage renal disease in the United States. *American Journal of Kidney Diseases*, *45*(SUPPL. 1).

Crews, D. C., Sozio, S. M., Liu, Y., Coresh, J., & Powe, N. R. (2011). Inflammation and the paradox of racial differences in dialysis survival. *Journal of the American Society of Nephrology*, *22*(12), 2279-2286.

Daugirdas, J. T., Blake, P. G., & Ing, T. S. (2012). *Handbook of dialysis*. Lippincott Williams & Wilkins.

Devins, G. M., Mann, J., Mandin, H., Paul, L. C., Hons, R. B., Burgess, E. D., ... & Buckle, S. (1990). Psychosocial predictors of survival in end-stage renal disease. *Journal of Nervous and Mental Disease*.

Dietz, K., Gail, M., Krickeberg, K., Samet, J., & Tsiatis, A. (2002). Statistics for Biology and Health. *Survival Analysis, Edition Springer*.

Einwohner, R., Bernardini, J., Fried, L., & Piraino, B. (2004). The effect of depressive symptoms on survival in peritoneal dialysis patients. *Peritoneal Dialysis International*, *24*(3), 256-263.

Fan, L., Sarnak, M. J., Tighiouart, H., Drew, D. A., Kantor, A. L., Lou, K. V., ... & Weiner, D. E. (2014). Depression and all-cause mortality in hemodialysis patients. *American journal of nephrology*, *40*(1), 12-18.

Fenton, S. S., Schaubel, D. E., Desmeules, M., Morrison, H. I., Mao, Y., Copleston, P., ... & Kjellstrand, C. M. (1997). Hemodialysis versus peritoneal dialysis: a comparison of adjusted mortality rates. *American Journal of Kidney Diseases*, *30*(3), 334-342.

Feingold, E., Adams, J., Penprase, B., & Tubie, B. (2015). Effect of body mass index and albumin on mortality rates for adult African-American hemodialysis patients. *Journal of the American Association of Nurse Practitioners*, *27*(11), 637-645.

Fernández-Martín, J. L., Martínez-Camblor, P., Dionisi, M. P., Floege, J., Ketteler, M., London, G., ... & Bos, W. J. (2015). Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. *Nephrology Dialysis Transplantation*, *30*(9), 1542-1551.

Fischer, M. J., Porter, A. C., & Lash, J. P. (2013). Treatment of depression and poor mental health among patients receiving maintenance dialysis: are there options other than a pill or a couch?. *American Journal of Kidney Diseases*, *61*(5), 694-697

Floege, J., Gillespie, I. A., Kronenberg, F., Anker, S. D., Gioni, I., Richards, S., ... & Eckardt, K. U. (2015). Development and validation of a predictive mortality risk score from a European hemodialysis cohort. *Kidney international*, *87*(5), 996-1008.

Foley, R. N., Parfrey, P. S., Harnett, J. D., Kent, G. M., Murray, D. C., & Barre, P. E. (1996). Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney international*, *49*(5), 1379-1385.

Fried, L., Bernardini, J., & Piraino, B. (2001). Charlson comorbidity index as a predictor of outcomes in incident peritoneal dialysis patients. *American journal of kidney diseases*, *37*(2), 337-342.

Gardiner, J. C. (2010). Survival analysis: overview of parametric, nonparametric and semiparametric approaches and new developments. In *SAS Global Forum 2010. Statistics and Data Analysis*.

George, B., Seals, S., & Aban, I. (2014). Survival analysis and regression models. *Journal of Nuclear Cardiology*, *21*(4), 686-694.

Georgianos, P. I., & Agarwal, R. (2016). Epidemiology, diagnosis and management of hypertension among patients on chronic dialysis. *Nature Reviews Nephrology*, *12*(10), 636.

Ghaderian, S. B., Hayati, F., Shayanpour, S., & Mousavi, S. S. B. (2015). Diabetes and end-stage renal disease; a review article on new concepts. *Journal of renal injury prevention*, *4*(2), 28.

Goodkin, D. A., Bragg-Gresham, J. L., Koenig, K. G., Wolfe, R. A., Akiba, T., Andreucci, V. E., ... & Held, P. J. (2003). Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Journal of the American Society of Nephrology*, *14*(12), 3270-3277.

Gordis, L. (2013). Epidemiology. 5th. Elsevier Health Sciences.

Guyon, I., & Elisseeff, A. (2003). An introduction to variable and feature selection. *Journal of machine learning research*, *3*(Mar), 1157-1182.

Hall, Y. N., Choi, A. I., Xu, P., O'Hare, A. M., & Chertow, G. M. (2011). Racial ethnic differences in rates and determinants of deceased donor kidney transplantation. *Journal of the American Society of Nephrology*, ASN-2010080819.

Hemmelgarn, B. R., Manns, B. J., Quan, H., & Ghali, W. A. (2003). Adapting the Charlson Comorbidity Index for use in patients with ESRD. *American Journal of Kidney Diseases*, *42*(1), 125-132.

Hess, K. R. (1995). Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. *Statistics in medicine*, *14*(15), 1707-1723.

Hocher, B., Kalk, P., Godes, M., Liefeldt, L., Ziebig, R., Stasch, J. P., ... & Pfab, T. (2008). Gender-dependent impact of risk factors for cardiovascular and non-cardiovascular mortality in end-stage renal disease patients on haemodialysis. *Kidney and Blood Pressure Research*, *31*(5), 360-366.

Hsu, C. Y., McCulloch, C. E., Iribarren, C., Darbinian, J., & Go, A. S. (2006). Body mass index and risk for end-stage renal disease. *Annals of internal medicine*, *144*(1), 21-28.

Huang, C. C., Cheng, K. F., & Wu, H. D. I. (2008). Survival analysis: comparing peritoneal dialysis and hemodialysis in Taiwan. *Peritoneal Dialysis International*, *28*(Supplement 3), S15-S20.

Iseki, K., Miyasato, F., Tokuyama, K., Nishime, K., Uehara, H., Shiohira, Y., ... & Kowatari, T. (1997). Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. *Kidney international*, *51*(4), 1212-1217.

Johnson, J. G., Gore, S. M., & Firth, J. (1999). The effect of age, diabetes, and other comorbidity on the survival of patients on dialysis: a systematic quantitative overview of the literature. *Nephrology Dialysis Transplantation*, *14*(9), 2156-2164.

Jolly, S. E., Burrows, N. R., Chen, S. C., Li, S., Jurkovitz, C. T., Norris, K. C., & Shlipak, M. G. (2011). Racial and ethnic differences in mortality among individuals with chronic kidney disease: results from the Kidney Early Evaluation Program (KEEP). *Clinical Journal of the American Society of Nephrology*, *6*(8), 1858-1865.

Kalantar-Zadeh, K., Ikizler, T. A., Block, G., Avram, M. M., & Kopple, J. D. (2003). Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *American Journal of Kidney Diseases*, *42*(5), 864-881.

Kalantar-Zadeh, K., Kilpatrick, R. D., Kuwae, N., McAllister, C. J., Alcorn Jr, H., Kopple, J. D., & Greenland, S. (2005). Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. *Nephrology Dialysis Transplantation*, *20*(9), 1880-1888.

Kalantar-Zadeh, K., Kilpatrick, R. D., McAllister, C. J., Greenland, S., & Kopple, J. D. (2005). Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: the 58th annual fall conference and scientific sessions. *Hypertension*, *45*(4), 811-817.

Kalantar-Zadeh, K., Kopple, J. D., Block, G., & Humphreys, M. H. (2001). A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *American journal of kidney diseases*, *38*(6), 1251-1263.

Kalantar-Zadeh, K., Miller, J. E., Kovesdy, C. P., Mehrotra, R., Lukowsky, L. R., Streja, E., ... & Norris, K. C. (2010). Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. *Journal of Bone and Mineral Research*, *25*(12), 2724-2734.

Keane, W. F., & Collins, A. J. (1994). Influence of co-morbidity on mortality and morbidity in patients treated with hemodialysis. *American journal of kidney diseases*, *24*(6), 1010-1018.

Kestenbaum, B., Sampson, J. N., Rudser, K. D., Patterson, D. J., Seliger, S. L., Young, B., ... & Andress, D. L. (2005). Serum phosphate levels and mortality risk among people with chronic kidney disease. *Journal of the American Society of Nephrology*, *16*(2), 520-528.

Kim, H., Kim, K. H., Park, K., Kang, S. W., Yoo, T. H., Ahn, S. V., ... & Kim, S. J. (2014). A population-based approach indicates an overall higher patient mortality with peritoneal dialysis compared to hemodialysis in Korea. *Kidney international*, *86*(5), 991-1000.

Kimmel, P. L., Peterson, R. A., Weihs, K. L., Simmens, S. J., Alleyne, S., Cruz, I., & Veis, J. H. (1998). Psychosocial factors, behavioral compliance and survival in urban hemodialysis patients1. *Kidney international*, *54*(1), 245-254.

Kimmel, P. L., Peterson, R. A., Weihs, K. L., Simmens, S. J., Alleyne, S., Cruz, I., & Veis, J. H. (2000). Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney international*, *57*(5), 2093-2098.

Klarenbach, S. W., Tonelli, M., Chui, B., & Manns, B. J. (2014). Economic evaluation of dialysis therapies. *Nature Reviews Nephrology*, *10*(11), 644.

Kleinbaum, D. G., & Klein, M. (2006). Survival analysis: a self-learning text, Springer Science & Business Media.

Koch, M., Hollenbeck, M., Trapp, R., Kulas, W., & Grabensee, B. (2006). Value of Diabetes as an Independent Predictor of Death in Subjects with End-Stage Renal DiseaseBedeutung des Diabetes als unabhängiger Prädiktor für den Tod bei Patienten mit terminaler Niereninsuffizienz. *Medizinische Klinik*, *101*(12), 933-937.

Kochanek, K. D., Xu, J., Murphy, S. L., Minino, A. M., & Kung, H. C. (2011). National vital statistics reports. *National Vital Statistics Reports*, *59*(4), 1.

Kramer, H. J., Saranathan, A., Luke, A., Durazo-Arvizu, R. A., Guichan, C., Hou, S., & Cooper, R. (2006). Increasing body mass index and obesity in the incident ESRD population. *Journal of the American Society of Nephrology*, *17*(5), 1453-1459.

Kurella, M., Mapes, D. L., Port, F. K., & Chertow, G. M. (2006). Correlates and outcomes of dementia among dialysis patients: the Dialysis Outcomes and Practice Patterns Study. *Nephrology Dialysis Transplantation*, *21*(9), 2543-2548.

Lattouf, O. M., & Ricketts, R. R. (1986). Peritoneal dialysis in infants and children. *The American surgeon*, *52*(2), 66-69.

Lawton, P. D., Cunningham, J., Zhao, Y., Gray, N. A., Chatfield, M. D., Baade, P. D., ... & Jose, M. D. (2015). Survival of Indigenous Australians receiving renal replacement therapy: closing the gap?. *The Medical Journal of Australia*, *202*(4), 200-204.

Lee, S., Ryu, J. H., Kim, H., Kim, K. H., Ahn, H. S., Hann, H. J., ... & Choi, K. B. (2014). An assessment of survival among Korean elderly patients initiating dialysis: a national population-based study. *PloS one*, *9*(1), e86776.

Lee, C. C., Sun, C. Y., & Wu, M. S. (2009). Long-term modality-related mortality analysis in incident dialysis patients. *Peritoneal Dialysis International*, *29*(2), 182-190.

Liem, Y. S., Wong, J. B., Hunink, M. G. M., de Charro, F. T., & Winkelmayer, W. C. (2007). Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands. *Kidney international*, *71*(2), 153-158.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., ... & Aryee, M. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet*, *380*(9859), 2224-2260.

Lucas, M. F., Quereda, C., Teruel, J. L., Orte, L., Marcén, R., & Ortuño, J. (2003). Effect of hypertension before beginning dialysis on survival of hemodialysis patients. *American journal of kidney diseases*, *41*(4), 814-821.

Ma, J. Z., Ebben, J., Xia, H., & Collins, A. J. (1999). Hematocrit level and associated mortality in hemodialysis patients. *Journal of the American Society of Nephrology*, *10*(3), 610-619.

Madziarska, K., Weyde, W., Penar, J., Zukowska-Szczechowska, E., Krajewska, M., Golebiowski, T., ... & Klinger, M. (2013). Different mortality predictor pattern in hemodialysis and peritoneal dialysis diabetic patients in 4-year prospective observation. *Postepy Hig Med Dosw (Online)*, *67*, 1076-1082.

Mafra, D., Farage, N. E., Azevedo, D. L., Viana, G. G., Mattos, J. P., Velarde, L. G. C., & Fouque, D. (2007). Impact of serum albumin and body-mass index on survival in hemodialysis patients. *International urology and nephrology*, *39*(2), 619-624.

Marshall, M. R., Polkinghorne, K. R., Kerr, P. G., Agar, J. W., Hawley, C. M., & McDonald, S. P. (2015). Temporal changes in mortality risk by dialysis modality in the Australian and New Zealand dialysis population. *American Journal of Kidney Diseases*, *66*(3), 489-498.

Mazzuchi, N., Carbonell, E., & Fernández-Cean, J. (2000). Importance of blood pressure control in hemodialysis patient survival. *Kidney international*, *58*(5), 2147-2154.

Metcalfe, W., Khan, I. H., Prescott, G. J., Simpson, K., Macleod, A. M., & Scottish Renal Registry. (2003). End-stage renal disease in Scotland: outcomes and standards of care. *Kidney international*, *64*(5), 1808-1816.

Miskulin, D., Bragg-Gresham, J., Gillespie, B. W., Tentori, F., Pisoni, R. L., Tighiouart, H., ... & Port, F. K. (2009). Key comorbid conditions that are predictive of survival among hemodialysis patients. *Clinical Journal of the American Society of Nephrology*, *4*(11), 1818-1826.

Moore, D. F. (2016). *Applied survival analysis using R*. Cham: Springer.

Nordio, M., Limido, A., Maggiore, U., Nichelatti, M., Postorino, M., & Quintaliani, G. (2012). Survival in patients treated by long-term dialysis compared with the general population. *American Journal of Kidney Diseases*, *59*(6), 819-828.

Norris, K. C., Kalantar-Zadeh, K., & Kopple, J. D. (2011). The role of race in survival among patients undergoing dialysis. *Nephrology news & issues*, *25*(13), 13.

Orbe, J., Ferreira, E., & Núñez-Antón, V. (2002). Comparing proportional hazards and accelerated failure time models for survival analysis. *Statistics in medicine*, *21*(22), 3493-3510.

Park, J. M., Lee, J. H., Jang, H. M., Park, Y., Kim, Y. S., Kang, S. W., ... & Lee, J. E. (2018). Survival in patients on hemodialysis: Effect of gender according to body mass index and creatinine. *PloS one*, *13*(5), e0196550.

Parkin, D. M., & Hakulinen, T. (1991). Analysis of survival. *Cancer Registration, Principles and Methods. IARC Scientific Publications*, (95), 159-176.

Perkovic, V., Huxley, R., Wu, Y., Prabhakaran, D., & MacMahon, S. (2007). The burden of blood pressure-related disease: a neglected priority for global health. *Hypertension*, *50*(6), 991-997.

Perl, J., Wald, R., McFarlane, P., Bargman, J. M., Vonesh, E., Na, Y., ... & Moist, L. (2011). Hemodialysis vascular access modifies the association between dialysis modality and survival. *Journal of the American Society of Nephrology*, *22*(6), 1113-1121.

Phelan, P. J., O'Kelly, P., Walshe, J. J., & Conlon, P. J. (2008). The importance of serum albumin and phosphorous as predictors of mortality in ESRD patients. *Renal failure*, *30*(4), 423-429.

Powe, N. R. (2008). Let's get serious about racial and ethnic disparities. *Journal of the American Society of Nephrology*, *19*(7), 1271-1275.

Prinja, S., Gupta, N., & Verma, R. (2010). Censoring in clinical trials: review of survival analysis techniques. *Indian journal of community medicine: official publication of Indian Association of Preventive & Social Medicine*, *35*(2), 217.

Purnama, D., Riono, P., & Farid, M. N. (2015). The Impact of Diabetes Mellitus and Hypertension As Comorbidon Survival Rate Chronic Kidney Disease on Chronic Hemodialysis Patients (INDONESIAN RENAL REGISTRY REPORT ANALYSIS 2007-2012). *Journal of Hypertension*, *33*, e13-e14.

Rahman, M., Fu, P., Sehgal, A. R., & Smith, M. C. (2000). Interdialytic weight gain, compliance with dialysis regimen, and age are independent predictors of blood pressure in hemodialysis patients. *American journal of kidney diseases*, *35*(2), 257-265.

Rakowski, D. A., Caillard, S., Agodoa, L. Y., & Abbott, K. C. (2006). Dementia as a predictor of mortality in dialysis patients. *Clinical Journal of the American Society of Nephrology*, *1*(5), 1000-1005.

Ricks, J., Molnar, M. Z., Kovesdy, C. P., Kopple, J. D., Norris, K. C., Mehrotra, R., ... & Kalantar-Zadeh, K. (2011). Racial and ethnic differences in the association of body mass index and survival in maintenance hemodialysis patients. *American Journal of Kidney Diseases*, *58*(4), 574-582.

Rosenthal Asher, D., Ver Halen, N., & Cukor, D. (2012). Depression and nonadherence predict mortality in hemodialysis treated end-stage renal disease patients. *Hemodialysis International*, *16*(3), 387-393.

Rostand, S. G., Kirk, K. A., & Rutsky, E. A. (1982). Relationship of coronary risk factors to hemodialysis-associated ischemic heart disease. *Kidney international*, *22*(3), 304-308.

Ryu, J. H., Kim, H., Kim, K. H., Hann, H. J., Ahn, H. S., Lee, S., ... & Ryu, D. R. (2015). Improving survival rate of Korean patients initiating dialysis. *Yonsei medical journal*, *56*(3), 666-675.

Salahudeen AK. (2003). Obesity and survival on dialysis. *American journal of kidney diseases*. *41(5):925-32*.

Sayin, B., Colak, T., Tutal, E., & Sezer, S. (2013). Comparison of preemptive kidney transplant recipients with nonpreemptive kidney recipients in single center: 5 years of follow-up. *International journal of nephrology and renovascular disease*, *6*, 95.

Schroijen, M. A., van de Luijtgaarden, M. W. M., Noordzij, M., Ravani, P., Jarraya, F., Collart, F., ... & Wanner, C. (2013). Survival in dialysis patients is different between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. *Diabetologia*, *56*(9), 1949-1957.

Sens, F., Schott-Pethelaz, A. M., Labeeuw, M., Colin, C., & Villar, E. (2011). Survival advantage of hemodialysis relative to peritoneal dialysis in patients with end-stage renal disease and congestive heart failure. *Kidney international*, *80*(9), 970-977.

Serafinceanu, C., Neculaescu, C., Cimponeriu, D., Timar, R., & Covic, A. C. (2014). Impact of gender and dialysis modality on early mortality risk in diabetic ESRD patients: data from a large single center cohort. *International urology and nephrology*, *46*(3), 607-614.

Shabankhani, B., Kazemnejad, A., Zaeri, F., Espahbodi, F., Ahmadi, M. H., & Mirkazemi, R. (2016). Survival Factors in Patients With End-stage Renal Disease in Mazandaran Province, Iran. *Iranian journal of kidney diseases*, *10*(2), 79.

Singh, R., & Mukhopadhyay, K. (2011). Survival analysis in clinical trials: Basics and must know areas. *Perspectives in clinical research*, *2*(4), 145.

Smith, T., & Smith, B. (2003). Kaplan-Meier And Cox Proportional Hazards Modeling: Hands On Survival Analysis. *SAS® Users Group International Proc. Seattle, Washington*.

Sood, M. M., Hemmelgarn, B., Rigatto, C., Komenda, P., Yeates, K., Promislow, S., ... & Tangri, N. (2012). Association of modality with mortality among Canadian Aboriginals. *Clinical Journal of the American Society of Nephrology*, *7*(12), 1988-1995.

Soucie, J. M., & McClellan, W. M. (1996). Early death in dialysis patients: risk factors and impact on incidence and mortality rates. *Journal of the American Society of Nephrology*, *7*(10), 2169-2175.

Speakman, J. R., & Westerterp, K. R. (2010). Reverse epidemiology, obesity and mortality in chronic kidney disease: modelling mortality expectations using energetics. *Blood purification*, *29*(2), 150-157.

Streja, E., Kovesdy, C. P., Molnar, M. Z., Norris, K. C., Greenland, S., Nissenson, A. R., ... & Kalantar-Zadeh, K. (2011). Role of nutritional status and inflammation in higher survival of African American and Hispanic hemodialysis patients. *American Journal of Kidney Diseases*, *57*(6), 883-893.

Tentori, F., Hunt, W. C., Rohrscheib, M., Zhu, M., Stidley, C. A., Servilla, K., ... & Zager, P. G. (2007). Which targets in clinical practice guidelines are associated with improved survival in a large dialysis organization?. *Journal of the American Society of Nephrology*, *18*(8), 2377-2384.

Terawaki, H., Matsuyama, Y., Matsuo, N., Ogura, M., Mitome, J., Hamaguchi, A., ... & Hosoya, T. (2012). A lower level of reduced albumin induces serious cardiovascular incidence among peritoneal dialysis patients. *Clinical and experimental nephrology*, *16*(4), 629-635.

Therneau, T. M., & Grambsch, P. M. (2013). *Modeling survival data: extending the Cox model*. Springer Science & Business Media.

Thijssen, S., Usvyat, L., & Kotanko, P. (2012). Prediction of mortality in the first two years of hemodialysis: results from a validation study. *Blood purification*, *33*(1-3), 165-170.

Tonelli, M., Wiebe, N., Culleton, B., House, A., Rabbat, C., Fok, M., ... & Garg, A. X. (2006). Chronic kidney disease and mortality risk: a systematic review. *Journal of the American Society of Nephrology*, *17*(7), 2034-2047.

Tong, J., Liu, M., Li, H., Luo, Z., Zhong, X., Huang, J., ... & Fu, J. (2016). Mortality and associated risk factors in dialysis patients with cardiovascular disease. *Kidney and Blood Pressure Research*, *41*(4), 479-487.

Valderrábano, F., Jofre, R., & López-Gómez, J. M. (2001). Quality of life in end-stage renal disease patients. *American Journal of Kidney Diseases*, *38*(3), 443-464.

Vijayan, M., Radhakrishnan, S., Abraham, G., Mathew, M., Sampathkumar, K., & Mancha, N. P. (2016). Diabetic kidney disease patients on hemodialysis: a retrospective survival analysis across different socioeconomic groups. *NDT Plus*, *9*(6), 833-838.

Wagner, M., Ansell, D., Kent, D. M., Griffith, J. L., Naimark, D., Wanner, C., & Tangri, N. (2011). Predicting mortality in incident dialysis patients: an analysis of the United Kingdom Renal Registry. *American Journal of Kidney Diseases*, *57*(6), 894-902.

Wang, I. K., Kung, P. T., Kuo, W. Y., Tsai, W. C., Chang, Y. C., Liang, C. C., ... & Wang, K. Y. (2013). Impact of dialysis modality on the survival of end-stage renal disease patients with or without cardiovascular disease. *Congestive heart failure*, *414*, 414-90.

Wang, I. K., Liang, W. M., Lin, C. L., Liu, Y. L., Chang, C. T., Yen, T. H., ... & Sung, F. C. (2016). Impact of dialysis modality on the survival of patients with end-stage renal disease and prior stroke. *International urology and nephrology*, *48*(1), 139-147.

Wen, C. P., Cheng, T. Y. D., Tsai, M. K., Chang, Y. C., Chan, H. T., Tsai, S. P., ... & Wen, S. F. (2008). All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *The Lancet*, *371*(9631), 2173-2182.

Wetmore, J. B., Phadnis, M. A., Ellerbeck, E. F., Shireman, T. I., Rigler, S. K., & Mahnken, J. D. (2014). Relationship between stroke and mortality in dialysis patients. *Clinical Journal of the American Society of Nephrology*, CJN-02900314.

Wong, M. D., Shapiro, M. F., Boscardin, W. J., & Ettner, S. L. (2002). Contribution of major diseases to disparities in mortality. *New England Journal of Medicine*, *347*(20), 1585-1592.

Wong, B., Ravani, P., Oliver, M. J., Holroyd-Leduc, J., Venturato, L., Garg, A. X., & Quinn, R. R. (2017). Comparison of Patient Survival Between Hemodialysis and Peritoneal Dialysis Among Patients Eligible for Both Modalities. *American Journal of Kidney Diseases*.

Xia, X., Zhao, C., Luo, Q., Zhou, Q., Lin, Z., Guo, X., ... & Huang, F. (2017). Nomogram for Predicting Cardiovascular Mortality in Incident Peritoneal Dialysis Patients: An Observational Study. *Scientific reports*, *7*(1), 13889.

Yan, G., Norris, K. C., Alison, J. Y., Ma, J. Z., Greene, T., Yu, W., & Cheung, A. K. (2013). The relationship of age, race, and ethnicity with survival in dialysis patients. *Clinical Journal of the American Society of Nephrology*, *8*(6), 953-961.

Yang, F., Khin, L. W., Lau, T., Chua, H. R., Vathsala, A., Lee, E., & Luo, N. (2015). Hemodialysis versus peritoneal dialysis: a comparison of survival outcomes in South-East Asian patients with end-stage renal disease. *PloS one*, *10*(10), e0140195.

Yang, W. C., Hwang, S. J., & Taiwan Society of Nephrology. (2008). Incidence, prevalence and mortality trends of dialysis end-stage renal disease in Taiwan from 1990 to 2001: the impact of national health insurance. *Nephrology dialysis transplantation*, *23*(12), 3977-3982.

Yeates, K., Zhu, N., Vonesh, E., Trpeski, L., Blake, P., & Fenton, S. (2012). Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. *Nephrology Dialysis Transplantation*, *27*(9), 3568-3575.

Zager, P. G., Nikolic, J., Brown, R. H., Campbell, M. A., Hunt, W. C., Peterson, D., ... & Johnson, H. K. (1998). "U" curve association of blood pressure and mortality in hemodialysis patients. *Kidney international*, *54*(2), 561-569.

Appendices

Appendix A- Context data

ref	Aim of the study	Publication date
Huang et al.	Comparing survival in patients on PD/HD modalities, estimating survival rate and mortality hazard in PD and HD patients in Taiwan	2008
Andrikos et al.	Comparing survival rate between PD and HD modalities.	2008
Lee et al.	Analysing modality-related mortality in long term among PD and HD dialysis patients (identifying impact of different modalities on morality).	2009
Sens et al.	Comparing survival outcome between HD and PD in ESRD patients with CHF	2011
Sood et al.	Explore the effect of type of modality (PD, HD) on all-cause mortality among Aboriginal and Caucasian patients and also to investigate survival rate among them. Examine potential differences by type of modality among two groups of patients' in Canada: Aboriginal and Caucasian	2012
Yeates et al.	Comparing and studying PD survival outcome relative to HD in Canada,	2012
Choi et al.	Examining the impact of modality on survival, comparing survival in two groups of dialysis patients (HD,PD)	2013
Madziarska et al.	Identifying factors that have a significant impact on survival, identifying differences in the efficiency of PD and HD modalities	2013
Wang et al.	Comparing survival rate in PD and HD in incident ESRD patients with CAD or CHF	2013
Kim et al.	Comparing survival between incident HD and PD dialysis patients	2014
Serafinceanu et al.	Identify predictors (clinical and demographic ones) that significantly associate with early mortality in diabetic patients who are incident to dialysis	2014
Marshall et al.	Comparing and examining temporal changes in survival among patients undergoing facility HD, home HD and PD. Examining the era effect in dialysis population in which change in mortality risk with dialysis modality over time accounting for patient, treating center, competing risk of transplantation.	2015
Yang et al.	comparing the survival outcome of ESRD patients on different modalities (HD/PD)	2015
Wang et al.	Comparing survival between HD and PD in ESRD patients with prior stroke	2016

Appendix B- Quantitative and qualitative findings

Study	Main findings	Significant variables	Survival rate			
Sood et al. (2008)	Type of modality affects Aboriginal patients' survival. This group on PD experience higher rate of mortality and technique failure compared to Caucasian. Risk of mortality and technique failure is higher among younger (under 50) patients undergoing PD dialysis.	Age as a significant modifier, race X modality	1 year, 2-year, 5-year, 8-year, 10-year (Aboriginal-Caucasian)			
			HD:		PD:	
			0.83	0.83	0.95	0.98
			0.63	0.63	0.84	0.86
			0.4	0.42	0.61	0.68
			0.27	0.3	0.47	0.56
			0.2	0.28	0.35	0.5
Serafinceanu et al. (2014)	Hemodialysis used as a first/single method for RRT and the LI of dialysis were identified as the significant factors that affect survival	the use of HD and the Late initiation of dialysis	1 year, 2-year, 3-year, 4-year, 5-year			
			PD: 0.3 0.22 0.1		HD: 0.22 0.17 0.07	
Yang et al. (2015)	Risk of mortality is reported higher among incident dialysis patients initiate PD dialysis compared to that of incident dialysis patients undergoing HD	PD modality, age group, diabetes, cardiovascular disease	5-year survival (whole cohort, propensity score matched subsample):			
			PD:		HD:	
			0.2	0.2	0.62	0.5
Huang et al. (2008)	Age, comorbidities condition, diabetes and gender are the most significant modifiers of the impact of modality on survival outcome. Survival outcome is the same for PD and HD patients in long term. Older patients with diabetes have a better survival on HD.	Age, sex, comorbid conditions, primary renal disease (DM, vs non-DM)	1 year, 2-year, 3-year, 5-year, 7-year, 10-year			
			PD: 0.898 0.776 0.676 0.555 0.479 0.35		HD: 0.875 0.766 0.681 0.543 0.442 0.338	
Marshall et al. (2015)	Better survival among PD patients compared to home HD.	n/a	1 year, 2-year, 3-year, 4-year, 5-year			
			PD: 0.95 0.85 0.7 0.6 0.45		HD: 0.9 0.8 0.7 0.6 0.5	
Choi et al. (2013)	-Patients under 65 years without diabetes have a better survival under PD than HD. Patients after 90 days of dialysis initiation whether PD or	Older age, lower BMI, and fewer comorbidities,	6-month, 1-year, 18-month, 2-year survival			

			PD:	HD:
	HD showed similar survival outcome. 37% lower risk of mortality among PD patients compared to HD (Cox model). 51% lower risk of mortality patients under PD compared to HD.	including congestive heart failure and peptic ulcer disease	PD: 0.993 0.969 0.958 0.943	HD: 0.989 0.941 0.906 0.876
Yeates et al. (2012)	Similar survival outcome for both HD and PD modalities.	n/a	1-year survival, 2 year survival, 4-year, 5years	
			PD: 0.9 0.72 0.6 0.45 0.38	HD: 0.85 0.72 0.66 0.55 0.4
Kim et al. (2014)	Higher rate of mortality among PD dialysis patients than in HD modality (before and after applying propensity score matched group). Among older patients (>55 years) the mortality rate consistently higher in PD. While in the younger group no significant difference in the mortality rate has been shown	Age at the initiation of dialysis,	1-year, 2-year, 3-year, 4-year	
			PD: 0.90 0.79 0.71 0.6	HD: 0.87 0.78 0.72 0.63
Madziarska et al. (2013)	Type of modality does not impact on survival outcome. Elevated cholesterol level associates with better survival in HD patients. Advanced age associates with worse survival in PD patients.	Serum Albumin (whole population) Cholesterol level (HD) Age (PD)	1 year, 2-year, 3-year, 4-year	
			PD: 0.7 0.5 0.44 0.33	HD: 0.87 0.58 0.42 0.33
Lee et al. (2009)	Rate of mortality was not significantly different in PD and HD group. Dialysis modality has no significant impact on all-cause or infectious related mortality	n/a	1 year, 2-year, 3-year, 4-year, 5-year	
			PD: 0.9 0.8 0.78 0.7 0.63	HD: 0.95 0.85 0.8 0.75 0.68
Wang et al. (2013)	PD modality is associated with poorer survival among ESRD patients with CVD or diabetes compared to PD. Both non-diabetic and diabetic patients undergoing PD dialysis modality with or without CAD or CHF, have poorer survival outcome.	Gender, Comorbidities such as CAD, CHF, neoplasm, chronic hepatitis, cerebrovascular disease and chronic obstructive pulmonary disease	1 year, 2-year, 3-year, 4-year, 5-year, 6-year. 7-year, 8-year, 9-year, 10 year	
			PD: 0.95 0.91 0.86 0.82 0.79 0.74 0.70 0.66	HD: 0.93 0.88 0.83 0.80 0.77 0.73 0.69 0.66

Study	Findings	Covariates	Time points	PD		HD	
				0.62 0.58		0.63 0.61	
Sens et al. (2011)	PD was associated with higher rate of mortality in all sub groups. Rate of cardiovascular death was higher in PD dialysis patients.	age, NYHA stage III–IV CHF, CVC use at first dialysis session, PVD, liver cirrhosis, and behavior disturbance	1 year, 2-year, 3-year, 4-year, 5-year	PD: 0.68 0.43 0.3 0.23 0.16		HD: 0.73 0.6 0.5 0.4 0.3	
Wang et al. (2016)	Overall survival is poorer for patients with diabetes and prior stroke undergoing PD. Similar outcome for both HD and PD modality among non-diabetic patients with stroke. Gender is the main contributor to the mortality differences among PD and HD patients.	Gender, diabetes	1 year, 2-year, 3-year, 4-year, 5-year	PD: 0.83 0.67 0.54 0.44 0.35		HD: 0.81 0.63 0.59 0.47 0.41	
Andrikos et al. (2008)	Using AT approach, patients undergoing PD have better survival. Using ITT approach, similar outcome for both modalities.	n/a	1 year, 2-year, 3-year, 4-year, 5-year, (AT, ITT)	PD: 0.94 0.82 0.79 0.79	0.89 0.77 0.57 0.55	HD: 0.92 0.8 0.55 0.57	0.94 0.57 0.53 0.51

Appendix C- Cohort summary

ref	Cohort size/incident on modalities			Dataset	Follow-up duration	Modality condition	Study design
Sood et al. (2012)	31576			Canadian Organ Replacement Registry (CORR)	January 1, 2000 to December of 2009	Assigned modality after 90 days dialysis initiation	Intention to treat analysis retrospective
	HD Aboriginal=1839 Caucasian=21430	PD Aboriginal=554 Caucasian=6769					
Serafinceanu et al. (2014)	788			Dialysis Center of NIDNMD Paulescu, Bucharest	January 1996 to December 2005		Retrospective case-control study
Yang et al. (2015)	871			National University Hospital (NUH), Singapore	2005-2010	survived the first 90 days of dialysis	Observational prospective
	HD= 641	PD=230					
Huang et al. (2008)	48629			Taiwan Renal Registry	1995-2002	survived for the first 90 days on dialysis	Retrospective (intention-to-treat paradigm)
	HD=45820	PD=2809					
Marshall et al. (2015)	37552			The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).	March 31, 1998 - December 31, 2012.	n/a	observational inception cohort study- as treated paradigm prospective
	Facility HD: 20890	PD: 13220	Home HD: 3442				
Choi et al. (2013)	1060			Data was collected from 31 hospitals affiliated with CRC	September 1, 2008 and June 30, 2011	Modality defined as 90 days after the first dialysis	nationwide prospective observational (intention-to-treat analysis)
	HD: 736	PD= 324					
Yeates et al. (2012)	46839			Canadian Organ Replacement Register (CORR)	1991-2004 With follow-up to 2007	Initial modality considered as modality 90 days after the first service date	Intention to treat analysis (PH-model) As-treated (non PH-model)
	HD: 32531	PD: 14308					
Kim et al. (2014)	32280			Korean Health Insurance Review & Assessment Service database	26.5 month (2005-2008)	Survived more than 90 after dialysis initiation	Intention to treat analysis
	HD:24399	PD: 7881					

Madziarska et al. (2013)	61		three dialysis centers in south-west Poland	2006-2010	Being on maintance dialysis for at least 60 days	Prospective
	PD:26	HD:35				
Lee et al. (2009)	1347		Chang Gung Memorial Hospital, Keelung, Taiwan	May 1991 and October 2005	Being on dialysis for more than 90 days	Prospective study in a single center
	PD: 258	HD: 1089				
Wang et al. (2013)	35664		National Health Insurance Research Database (NHIRD)	1997 to 2007	Dialysis modality at day 90	Retrospective matched cohort study
	PD: 5944	HD: 29720				
Sens et al. (2011)	4401		French Renal Epidemiology and Information Network (REIN) Registry	2002 to 2008	modality at day 90 after first dialysis or the one at dialysis initiation if death occurred before the 90th day.	Prospective
	PD:933	HD:3468				
Wang et al. (2016)	2857		National Health Insurance Research Database (NHIRD)	2000 to 2010	Undergoing dialysis for at least 90 days	Retrospective
	PD: 982	HD: 1875				
Andrikos et al. (2008)	94		Nephrology department, G. Hatzikosta general hospital, Ioannina, Greece	January 1995 to December 2000	Being survived at least 90 days	Retrospective (AT and ITT analysis)
	PD: 48	HD: 46				

Appendix D- executive summary of evidence for survival outcome

	1-year		2-year		3-year		4-year		5-year	
	PD	HD	PD	HD	PD	HD	PD	HD	PD	HD
Sood et al. (2008)	0.95	0.83	0.84	0.63	0.61	0.4	0.47	0.27	0.35	0.2
Serafinceanu et al. (2014)	0.1	0.07	-	-	-	-	-	-	-	-
Yang et al. (2015)	0.8	0.9	0.65	0.8	0.4	0.73	0.28	0.7	0.2	0.62
Huang et al. (2008)	0.89	0.87	0.77	0.76	0.67	0.68	0.6	0.6	0.55	0.54
Marshall et al. (2015)	0.95	0.9	0.85	0.8	0.7	0.7	0.6	0.6	0.45	0.5
Choi et al. (2013)	0.96	0.94	0.94	0.87	-	-	-	-	-	-
Yeates et al. (2012)	0.9	0.85	0.72	0.72	0.6	0.66	0.45	0.55	0.38	0.4
Kim et al. (2014)	0.9	0.87	0.79	0.78	0.71	0.72	0.6	0.63	-	-
Madziarska et al. (2013)	0.7	0.87	0.5	0.58	0.44	0.42	0.33	0.33	-	-
Lee et al. (2009)	0.9	0.95	0.8	0.85	0.78	0.8	0.7	0.75	0.63	0.68
Wang et al. (2013)	0.95	0.93	0.91	0.88	0.86	0.83	0.82	0.8	0.79	0.77
Sens et al. (2011)	0.68	0.73	0.43	0.6	0.3	0.5	0.23	0.4	0.16	0.3
Wang et al. (2016)	0.83	0.81	0.67	0.63	0.54	0.59	0.44	0.47	0.35	0.41
Andrikos et al. (2008)	0.94	0.92	0.82	0.8	-	-	0.79	0.57	0.79	0.55

Appendix E- Ethic approval

TRI-HOSPITAL RESEARCH ETHICS BOARD (THREB)

(A shared service for Cambridge Memorial Hospital, Grand River Hospital and St. Mary's General Hospital)
Grand River Hospital, Rm. 615, Kaufman Building, 835 King Street West, Kitchener, Ontario, N2G 1G3
Tel: (519) 749-4300 ext. 5367 Fax: (519) 749- 4250

March 7, 2018   THREB #2017-0619

Dr. Helen Chen
C/o Kim Hendricks
University of Waterloo
Faculty of Applied Health Sciences
School of Public Health and Health Systems
200 University Ave. West
Waterloo, ON. N2L 3G1

Dear Helen Chen,
THREB#2017-0619 Patient Decisions regarding dialysis: a review of factors associated with survival and attrition in dialysis patients. Kim Hendricks GRH Co. UW

Study Identification Number: THREB #2017-0619
Initial Approval Date: February 15, 2017
Anniversary for Renewal: February 15, 2019

Thank you for your Annual Status Report requesting continuation of the above study for another year.

The Annual Status Report and request for renewal for the above study was reviewed at a full board meeting of the Tri-Hospital Research Ethics Board on **March 7, 2018** and is considered acceptable for a one year continuation. The study will be reviewed prior to the Anniversary for Renewal indicated above by the Tri-Hospital Research Ethics Board.

Sincerely,

Michael D. Coughlin, Ph.D.
Chair, Tri-Hospital Research Ethics Board

Cc: Karen Pieters, Julie Joza

Appendix F- Log-rank test (age categories)

	Number of patients	Observed	Expected	(O-E)^2/E	(O-E)^2/V
Age					
18-44	80	8	42.4	27.95	32.83
45-54	78	11	32.7	14.43	16.18
55-64	156	56	68.6	2.31	2.99
65-74	227	98	86.2	1.63	2.27
>75	217	134	77.1	42.05	56.45
	Chisq= 89.1 on 4 degrees of freedom, p= 0				

Appendix G- Log-rank test (gender)

	Log-Rank test				
	Number of patients	Observed	Expected	(O-E)^2/E	(O-E)^2/V
Gender					
male	453	184	175	0.48	1.25
female	270	100	109	0.769	1.25
	Chisq= 1.3 on 1 degrees of freedom, p= 0.263				

Appendix H- Log-rank test (modality)

	Number of patients	Observed	Expected	(O-E)^2/E	(O-E)^2/V
Modality					
HD	592	238	233.3	0.0949	0.536
PD	131	46	50.7	0.4366	0.536
	Chisq= 0.5 on 1 degrees of freedom, p= 0.464				

Appendix I- Backward elimination procedure

Step	Variables	Adjusted HR	95% CI		P-value
1					
	Age	1.05	1.04	1.06	<0.001
	Gender	0.86	0.67	1.11	0.239
	Modality	0.88	0.64	1.22	0.450
	Dementia	0.79	0.50	1.27	0.331
	Bipolar	1.95	0.83	4.61	0.127
	Depression	1.04	0.79	1.36	0.789
	HTN	0.62	0.41	0.93	0.020
	Cardiac disease	0.91	0.68	1.22	0.542
	CVA	0.94	0.72	1.23	0.673
	MI	0.88	0.66	1.19	0.416
	Lung disease	1.21	0.92	1.59	0.170
	Diabetes	1.12	0.86	1.47	0.386
	Cancer	0.95	0.74	1.22	0.664
2					
	Age	1.05	1.04	1.06	<0.001
	Gender	0.86	0.67	1.10	0.239
	Modality	0.88	0.64	1.22	0.454
	Dementia	0.80	0.50	1.27	0.344
	Bipolar	1.99	0.85	4.65	0.112
	HTN	0.62	0.41	0.93	0.021
	Cardiac disease	0.92	0.68	1.22	0.551
	CVA	0.94	0.72	1.24	0.675
	MI	0.88	0.66	1.19	0.417
	Lung disease	1.22	0.93	1.59	0.153
	Diabetes	1.13	0.86	1.47	0.379
	Cancer	0.94	0.73	1.21	0.654
3					
	Age	1.05	1.04	1.06	<0.001
	Gender	0.86	0.67	1.11	0.251
	Modality	0.88	0.64	1.22	0.439

Dementia	0.79	0.50	1.25	0.306
Bipolar	1.97	0.84	4.60	0.117
HTN	0.61	0.41	0.92	0.018
Cardiac disease	0.91	0.68	1.22	0.535
MI	0.88	0.66	1.19	0.404
Lung disease	1.21	0.93	1.58	0.162
Diabetes	1.12	0.86	1.47	0.389
Cancer	0.95	0.74	1.22	0.669

4

Age	1.05	1.04	1.06	<0.001
Gender	0.87	0.68	1.11	0.256
Modality	0.89	0.64	1.22	0.455
Dementia	0.79	0.50	1.25	0.305
Bipolar	1.97	0.85	4.61	0.116
HTN	0.62	0.41	0.92	0.019
Cardiac disease	0.91	0.68	1.21	0.519
MI	0.88	0.65	1.18	0.387
Lung disease	1.21	0.93	1.59	0.155
Diabetes	1.13	0.87	1.47	0.377

5

Age	1.05	1.04	1.06	<0.001
Gender	0.86	0.67	1.10	0.240
Modality	0.88	0.64	1.21	0.433
Dementia	0.78	0.50	1.24	0.303
Bipolar	1.94	0.83	4.53	0.124
HTN	0.60	0.40	0.90	0.012
MI	0.84	0.65	1.09	0.183
Lung disease	1.20	0.92	1.57	0.172
Diabetes	1.12	0.86	1.46	0.404

6

Age	1.05	1.04	1.06	<0.001
Gender	0.86	0.67	1.10	0.240
Dementia	0.80	0.51	1.26	0.336
Bipolar	1.95	0.83	4.54	0.123
HTN	0.60	0.40	0.89	0.012
MI	0.84	0.65	1.09	0.191
Lung disease	1.21	0.93	1.57	0.164
Diabetes	1.11	0.85	1.44	0.451

7

Age	1.05	1.04	1.06	<0.001
Gender	0.86	0.67	1.11	0.241
Dementia	0.80	0.51	1.27	0.343
Bipolar	1.99	0.86	4.64	0.109
HTN	0.62	0.42	0.92	0.016
MI	0.85	0.65	1.10	0.207
Lung disease	1.21	0.93	1.58	0.150

8

Age	1.05	1.04	1.06	<0.001
Gender	0.87	0.68	1.11	0.258
Bipolar	1.80	0.79	4.09	0.159
HTN	0.61	0.42	0.90	0.012
MI	0.85	0.66	1.11	0.232
Lung disease	1.23	0.94	1.60	0.128

9

Age	1.05	1.04	1.06	<0.001
Bipolar	1.76	0.78	3.98	0.177
HTN	0.63	0.43	0.92	0.017
MI	0.87	0.67	1.12	0.278
Lung disease	1.22	0.94	1.59	0.140

10

Age	1.05	1.04	1.06	<0.001
Bipolar	1.74	0.77	3.94	0.184
HTN	0.62	0.43	0.91	0.013
Lung disease	1.21	0.93	1.58	0.154

11

Age	1.05	1.04	1.06	<0.001
HTN	0.63	0.43	0.91	0.015
Lung disease	1.20	0.92	1.56	0.173

12

Age	1.05	1.04	1.06	<0.001
HTN	0.65	0.45	0.94	0.023

Glossary

ACR	Albumin to Creatinine Ratio "The first method of preference to detect elevated protein; ACR is calculated by dividing albumin concentration in milligrams by creatinine concentration in grams."[1]
BMI	Body Mass Index "An indicator of body density as determined by the relationship of body weight to body height. BMI=weight (kg)/height squared (m2)."[2]
CAD	Coronary Artery Disease "Pathological processes of coronary arteries that may derive from a congenital abnormality, atherosclerotic, or non-atherosclerotic cause."[3]
CAPD	Continuous Ambulatory Peritoneal Dialysis "Portable peritoneal dialysis using the continuous (24 hours a day, 7 days a week) presence of peritoneal dialysis solution in the peritoneal cavity except for periods of drainage and instillation of fresh solution."[4]
CCPD	Continuous Cycling Peritoneal Dialysis "A type of dialysis in which the patient is attached to an automatic cycler for short exchanges while sleeping at night. Mobility is not feasible because of the cumbersome equipment. During waking hours the patient receives long dialysis exchanges but has ambulatory freedom."[5]
CHF	Congestive Heart Failure "Heart failure in which the heart is unable to maintain adequate circulation of blood in the tissues of the body or to pump out the venous blood returned to it by the venous circulation"[6]
CI	Confidence Interval "A confidence interval gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data."[7]
CKD	Chronic Kidney Disease "Conditions in which the kidneys perform below the normal level for more than three months. Chronic kidney insufficiency is classified by five stages according to the decline in Glomerular Filtration Rate and the degree of kidney damage."[8]
CORR	Canadian Organ Replacement Register

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[1] National Kidney Foundation, (2017). Retrieved from:
https://www.kidney.org/kidneydisease/siemens_hcp_acr

[2] Body Mass Index. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-b/body-mass-index.html

[3] Coronary Artery Disease. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-c/coronary-artery-disease.html

[4] Continuous Ambulatory Peritoneal Dialysis. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-p/peritoneal-dialysis-continuous-ambulatory.html

[5] Continuous Cycling Peritoneal Dialysis. (2009). In *Medical dictionary online*. Retrieved from:
https://medical-dictionary.thefreedictionary.com/continuous+cycling+peritoneal+dialysis

[6] Congestive Heart Failure. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.merriam-webster.com/dictionary/congestive%20heart%20failure#medicalDictionary

[7] Confidence Interval. (n.d.). In Valerie J. Easton and John H. McColl's Statistics Glossary v1.1. Retrieved from:
http://www.stat.yale.edu/Courses/1997-98/101/confint.htm

[8] Chronic Kidney Disease. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-r/renal-insufficiency-chronic.html

CVA	Cerebrovascular Accident "The sudden death of some brain cells due to lack of oxygen when the blood flow to the brain is impaired by blockage or rupture of an artery to the brain. A CVA is also referred to as a stroke."[1]
DBP	Diastolic Blood Pressure "The lowest arterial blood pressure of a cardiac cycle occurring during diastole of the heart."[2]
DOPPS	Dialysis Outcomes and Practice Patterns Study
ESRD	End-Stage Renal Disease "The end-stage of chronic renal insufficiency. It is characterized by the severe irreversible kidney damage and the reduction in Glomerular Filtration Rate to less than 15 ml per min."[3]
GFR	Glomerular Filtration Rate "The volume of water filtered out of plasma through glomerular capillary walls into Bowman's capsules per unit of time. It is considered to be equivalent to insulin clearance."[4]
GRH	Grand River Hospital
GOF	Goodness of Fit "The conformity between an experimental result and theatrical expectation or between data and an approximating curve"[5]
HD	Hemodialysis "Separation of soluble substances and water from the blood by diffusion through a semipermeable membrane; separation of cellular elements and colloids from soluble substances is achieved by pore size in the membrane and rates of diffusion."[6]
HF	Hemofiltration "The process of removing blood from the living body (as of a kidney patient), purifying it by passing it through a system of extracorporeal filters, and returning it to the body."[7]
HR	Hazard Ratio "A theoretical measure of the probability of occurrence of an event per unit time at risk".[8]
HTN	Hypertension "Hypertension is high blood pressure. Blood pressure is the force of blood pushing against the walls of arteries as it flows through them. Arteries are the blood vessels that carry oxygenated blood from the heart to the body's tissues."[9]

[1] Cerebrovascular Accident. (n.d.). In *MedTerm dictionary*. Retrieved from:
https://www.medicinenet.com/script/main/art.asp?articlekey=2676
[2] Diastolic Blood Pressure. (n.d.). In *Merriam Webster Medical Dictionary*. Retrieved from:
https://www.merriam-webster.com/medical/diastolic%20blood%20pressure
[3] ESRD. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-k/kidney-failure-chronic.html
[4] Glomerular Filtration Rate. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-g/glomerular-filtration-rate.html
[5] Goodness of Fit. (n.d.). In *Merriam Webster Dictionary*. Retrieved from:
https://www.merriam-webster.com/dictionary/goodness%20of%20fit
[6] Hemodialysis. (n.d.). In *The free dictionary by Farlex*. Retrieved from:
https://medical-dictionary.thefreedictionary.com/haemodialysis
[7] Hemofiltration. (n.d.). In *Merriam Webster Medical Dictionary*. Retrieved from:
https://www.merriam-webster.com/medical/hemofiltration
[8] Hazard Ratio. (2014). In *A dictionary in Epidemiology)*. Retrieved from:
http://www.oxfordreference.com/view/10.1093/acref/9780199976720.001.0001/acref-9780199976720-e-2181
[9] Hypertension. (n.d.). In *The free dictionary by Farlex*. Retrieved from:

IHD	Ischemic Heart Disease "A pathological condition caused by lack of oxygen in cells of the myocardium."[1]	
NKF	National Kidney Foundation	
OR	Odds Ratio "A measure of association used in comparative studies, particularly case-control studies, that quantifies the association between an exposure and a health outcome; also called the cross-product ratio."[2]	
ORN	Ontario Renal Network	
PD	Peritoneal Dialysis "Dialysis fluid being introduced into and removed from the peritoneal cavity as either a continuous or an intermittent procedure."[3]	
PVD	Peripheral Vascular Disease "Pathological processes involving any one of the blood vessels in the vasculature outside the heart."[4]	
RRT	Renal Replacement Therapy "Procedures which temporarily or permanently remedy insufficient cleansing of body fluids by the kidneys."[5]	
SBP	Systolic Blood Pressure "the highest arterial blood pressure of a cardiac cycle occurring immediately after systole of the left ventricle of the heart".[6]	
USRDS	United States Renal Data System	

https://medical-dictionary.thefreedictionary.com/hypertension

[1] Ischemic Heart Disease. (2009). In *Mosby's Medical Dictionary*, 9th edition, Elsevier. Retrieved from:
https://medical-dictionary.thefreedictionary.com/ischemic+heart+disease

[2] Odds Ratio. (2014). In *Principles of Epidemiology in Public Health Practice, Third Edition, An Introduction to Applied Epidemiology and Biostatistics*. Retrieved from:
https://www.cdc.gov/ophss/csels/dsepd/ss1978/glossary.html

[3] Peritoneal dialysis. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-p/peritoneal-dialysis.html

[4] Peripheral Vascular Disease. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-p/peripheral-vascular-diseases.html

[5] Renal Replacement Therapy. (n.d.). In *Medical Dictionary Online*. Retrieved from:
https://www.online-medical-dictionary.org/definitions-r/renal-replacement-therapy.html

[6] Systolic Blood Pressure. (n.d.). In *Merriam Webster Medical Dictionary*. Retrieved from:
https://www.merriam-webster.com/medical/systolic%20blood%20pressure