Factors Associated with Dialysis Withdrawal in Chronic Dialysis Patients

by

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A thesis

presented to the University of Waterloo

in fulfilment of the

thesis requirement for the degree of

Master of Science

in

Public Health and Health Systems

Waterloo, Ontario, Canada, 2018

Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Background: Research on the factors associated with dialysis withdrawal in chronic dialysis patients has been limited. Authors and clinicians have used different definitions for dialysis withdrawal, resulting in inconsistent findings. This thesis explored the factors associated with dialysis withdrawal defined as "patient refused further treatment or voluntary withdrawal from the dialysis program" in chronic dialysis patients.

Methods: This retrospective study extracted patient information from the electronic renal patient management system *Nephrocare*™, and *ClinicalConnect*™ at the Grand River Hospital. A total of (N=723) patients who initiated chronic renal dialysis therapy (>30 days of duration) in renal dialysis program at Grand River Hospital (GRH), Ontario, during the period from 1st January, 2012 to 30th September, 2017 were consecutively included in the study. Patients with acute dialysis or patients receiving dialysis before the start of the study were excluded. Age, sex, modality, comorbidities such as diabetes, cardiac disease, hypertension, vascular disease, lung disease, malignancy, dementia, depression and bipolar disorder and aetiology of kidney disease were selected as hypothesis variables and duration of dialysis was the controlled variable in this study.

Results: The mean age of the sample was 64.86 years (±14.89) with 62.8% (*n*=454) males. The most common cause of renal disease was diabetes (33.6%) and the most common comorbidity was hypertension (94.5%). The mean duration of dialysis was 544.80 days (±486.83) days. The prevalence of dialysis withdrawal was 9.41% (*n*=68) with psychosocial (*n*= 16; 23.5%) being the

most common reason. The final logistic regression model showed that cardiac disease, [β= 0.6530; p=0.016], hypertension [β= 1.7421; p=0.019], dementia [β=1.1125; p=0.008] and age [β=0.0342; p=0.002] were significantly associated with dialysis withdrawal, with significant influence of duration of dialysis [β=-0.000841; p=0.0092] as a confounder on the above relationship.

Conclusion: The study showed age, cardiac disease, hypertension and dementia are significant predictors related to dialysis withdrawal in chronic dialysis population. The findings may help in identifying patients who are susceptible to dialysis withdrawal at the start of dialysis. Future researchers and nephrologists should design and conduct intervention studies focusing on strategies controlling the severity of comorbidities (cardiac disease and hypertension), regular assessment and monitoring of the progression of dementia, and other dialysis program changes to decrease dialysis withdrawal rates in chronic dialysis patients.

Key words:
Chronic dialysis, dialysis withdrawal, end-stage renal disease (ESRD), dialysis modality.

Acknowledgments

I would like to take this opportunity to thank those individuals who supported me to successfully complete this MSc program. First, I would like to thank Dr. Helen Chen. She has been an excellent supervisor who guided me throughout the two years of my MSc program. Her help in different steps of research work is commendable in terms of frequent meetings, suggestions, advice, feedback, and extensive readings. Her help was not restricted to my research and thesis, but she helped me in other aspect of work and personal issues. I would also like to thank my advisory committee, Dr. Ashok Chaurasia and Mr. Peter Varga for their guidance, suggestions and feedback throughout my research project, analysis, and in thesis writing. I would like to thank my research group colleagues namely Mahsa Ebad and Meng Zhu for their contribution in data collection and validation.

I would also like to thank my parents and family for their support, encouragement, love, and prayers. You are a source of inspiration and the reason behind my success and your support and encouragement has been my strength and asset.

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Chapter 1 Introduction and Overview

Chronic kidney disease (CKD) describes gradual loss of renal functions over a period of months or years and is classified into five stages, based on the measurement of estimated glomerular filtration rate (eGFR) (1, 2). The End Stage Renal Disease (ESRD) or CKD stage 5 represents the severe form of renal function, characterized by an eGFR of <15 mL/min/1.73m^2 and require maintenance dialysis or renal transplantation (1, 2). The prevalence of both CKD and dialysis is increasing globally, mainly because of long survival rates within this population. Canada has the third highest ESRD incident and prevalence rate after the US and Japan (3-7). The incidence of chronic dialysis in Ontario since 2010 is at a stable rate of 3.3% each year. In 2015, around 15,529 patients have advanced kidney disease, with 11,118 patients receiving chronic dialysis in Ontario[1]. There has been a slight increase in dialysis population from 22.3% to 24.8%, from 2009 to 2015. In 2015, 75% of patients were receiving in-facility dialysis, 19% were receiving peritoneal dialysis, and 6% were receiving home hemodialysis (8).

Despite the importance of dialysis for ESRD patients, previous studies have shown wide range in dialysis withdrawal (DW) rate ranging from 8% to 31% (9-12). Dialysis attrition, discontinuation or withholding, is one of the leading causes (12-26%) of death in ESRD patients in the US and Canada (13). Considering the need of dialysis in ESRD patients and a high

[1] Ontario Renal Network (ORN). CKD System Atlas, http://www.renalnetwork.on.ca/cms/one.aspx?objectId=353745&contextId=256223#.WzVf_dJKjIU, accessed on 2018-06-28

prevalence of dialysis withdrawal along with the associated morbidity and mortality, few authors have explored the factors associated with dialysis withdrawal.

Gessert et al. (2013) have found a significantly higher dialysis withdrawal rate in women vs men (26.3% vs. 23.0%); older age vs younger age (29.83% vs.18.14%) and white race vs black race (29.5% vs. 14.7%) (36). Factors such as diabetes-induced ESRD and renovascular disease were associated with increased rate of withdrawal (HR=1.58 and HR=1.26, respectively (11). Additionally, having a low BMI (Body Mass Index) <18.5 kg/m (HR=1.37), is associated with increased rates of withdrawal (11). Type of dialysis: PD (Peritoneal dialysis) and HD (Hemodialysis), comorbid conditions such as diabetes and cardiac diseases and laboratory values such as albumin, phosphate and hemoglobin are associated with dialysis withdrawal (10-13, 15, 17). However, few studies have also shown insignificant association between gender, BMI, socioeconomic predictors, comorbidities, aetiology of renal disease, albumin and creatinine, and type and duration of dialysis with dialysis withdrawal (10-17).

The scarcity of literature and the overall inconsistent and inconclusive findings warrants an in-depth exploration of the relationship to investigate predictors that might influence the rate of dialysis withdrawal and identify gaps in the literature, (with regards to the factors associated with dialysis withdrawal), in which original research is needed. In addition to identifying gaps in the literature, the proposed review will also help in identifying the possible reasons for the differences in findings by collating, summarizing, analyzing and synthesizing the research findings by drawing conclusions from the existing literature.

This thesis consists of the present chapter and six subsequent chapters. The present chapter provides an overview of chronic kidney disease, chronic dialysis and factors associated

with dialysis withdrawal. The next chapter presents literature review on the factors associated with withdrawal from the chronic dialysis. Chapter 3 provides a rationale to conduct an original research, and provide specific aims and objectives of the study. Chapter 4 includes a detailed description of the methods. Chapter 5 provides descriptive and regression results. Chapter 6 synthesizes the findings in relation to existing literature, identifies study strengths, limitations and advancement of knowledge transferrable into practice. The last chapter of this thesis provides implications of the study and conclusion with recommendation for further investigation.

Chapter 2 Literature Review

2.1 End-Stage Renal Disease (ESRD) and Dialysis

End Stage Renal Disease (ESRD) is the irreversible deterioration of kidney function and is defined by a glomerular filtration rate (GFR) of <15ml/min (normal is >60 ml/min) (1, 2). ESRD has multifactorial aetiology as a complication of diabetes mellitus, hypertension, autoimmune diseases and congenital abnormalities (19). There are nearly 700,000, 120,000 and 135,000 people with CKD stage 5 in the US, UK and Europe, respectively. The prevalence of ESRD in Saudi Arabia is 5.7% and 6% in Australia. Furthermore, from 2006-2012, Canada has the third highest ESRD incident rate and prevalence rate after the US and Japan (3-7).

The treatment of ESRD is maintenance dialysis or transplant, though in a small number of patients' life style changes and drug treatment may help (1, 2, 20). Dialysis is a treatment modality in which wastes and toxins are removed from the blood and is a treatment of choice following a significant damage to the kidneys (21-27). The first successful dialysis was initiated by Dr. Willem Kolff in a 67-year-old female in 1943. The first outpatient hemodialysis was performed by Belding Scribner in 1960, as a conventional (3 times a week) dialysis therapy. Later, Scribner developed a portable dialyzer, leading to 40% of the patients performing home dialysis by 1970 (21-27).

Currently, many dialysis treatment alternatives are available in ESRD patients as shown in Table 1. These modalities are dependent on whether dialysis performed at home or in-facility and based on the type (hemodialysis and peritoneal dialysis) frequency and

duration (acute or chronic) of dialysis. Hemodialysis (HD)is a dialysis modality in which a filter and dialysis machine is attached to the patient via catheter inserted in a major vein, usually in the patient's subclavian to remove waste and toxins from the blood stream and correct the electrolyte imbalance (8, 21-24, 28). Peritoneal dialysis (PD) is a dialysis treatment in which the cleansing fluid is inserted into the peritoneal cavity via catheter, the fluid filters the waste products and toxins from the blood, after some time the fluid along with the waste is removed via catheter and is discarded (8, 28, 29).

Table 1 Dialysis Treatment Modalities Available in End-Stage Renal Disease (ESRD) Population

Modality	Definition
Hemodialysis (HD)	Dialysis through blood
Peritoneal dialysis (PD)	Dialysis through peritoneal fluid
Acute or short term or transient dialysis	Dialysis <30 days
Chronic or long term dialysis[2]	Dialysis ≥30 days

Dialysis can be conventional the most common form), followed by daily and/or nocturnal (8, 26, 27). The type of peritoneal dialysis includes: Continuous Ambulatory

[2] Ontario Renal Network. CKD Data. Technical Information http://www.renalnetwork.on.ca/ckd_data/accountability_to_patients_data/techinfo/#.W0WkadJKjIU. accessed on 2018-07-11

Peritoneal Dialysis (CAPD) in which patient's abdominal cavity fluid is exchanged around 4 times/24 hours via an implanted peritoneal catheter and in Automated Peritoneal Dialysis (APD) or CCPD (Continuous Cycling PD), fluid exchange occurs at night which may be supplemented by additional day time fluid exchanges (8, 28, 29). Dialysis can also be classified as short-term transient or acute dialysis (<30 days) and long term or chronic dialysis (≥30 days) (8, 28, 29).

The prevalence of maintenance dialysis ranged from the lowest in China around 79 pmp (per million population) to the highest in Japan (2385 pmp). The incidence rates of maintenance dialysis ranged from 91 pmp in UK to 349 pmp in the US (30). The renal replacement therapy (RRT) is higher in Ontario than the national average of Canada; while the prevalence of CKD is the same. An estimated 11,200 patients in Ontario are on dialysis (8). The most prevalent is hemodialysis (76.3%), followed by peritoneal dialysis (18.1%) and home hemodialysis (5.6%) (8).

2.2 Factors Associated With Dialysis Withdrawal (DW)

Despite the availability of chronic dialysis programs, the morbidity and mortality in ESRD patients, remains high. There are many factors associated with survival models in ESRD patients including modifiable factors such as patient health status, BMI, serum urea, albumin and hemoglobin and non-modifiable factors such as age, gender and race and comorbidities (31-35). Dialysis attrition, discontinuation or withholding, is one of the leading causes (12-26%) of death in ESRD patients in the US and Canada (13, 14). However, in European countries, dialysis withdrawal, withholding or discontinuation is low, only 2–7% of all causes of deaths (13). Few authors have explored the relationship between demographic factors, overall health condition and

comorbidities, cause of ESRD; serum albumin and phosphorus, and duration and type of dialysis modality with dialysis withdrawal (9-13). Religion and cultural beliefs and ethnicity can also influence the withdrawal from dialysis (14).

2.2.1 Demographics

The relationship between demographic factors such as age, gender, race/ethnicity, residence, education, employment and marital status and dialysis withdrawal have been explored by few researchers in different geographical locations (9-11, 13, 15, 17, 18). Older age is associated with higher rate of dialysis withdrawal. Discontinuation of dialysis was more frequent in ≥ 70 years old patients versus < 70 years old (29.83% vs. 18.14%, $p < 0.001$) (36). Ellwood et al. (2013) found higher rates of withdrawal in patients older than 75 years old than their younger counterpart, and the increasing of age was significantly associated with DW (HR, 1.81; 95% CI, 1.75–1.88) (11). Findlay et al. (2016) also found the same association of older age with dialysis withdrawal (37). Older aged patients have multiple medical problems and comorbidities that worsens with increase duration of dialysis, with a rapid alteration in physical and mental health, leading to dialysis withdrawal and discontinuation of treatment (11, 13, 38).

Dialysis withdrawal varies with race and ethnicity, patient-based dialysis discontinuation was more frequent whites than blacks (29.5% vs. 14.7%, $p < 0.001$) or patients of other races (29.5% vs. 19.2%, $p < 0.001$) (36). Similarly, other authors have reported a higher rate of DW in white persons than African Americans and Asians (36, 39-43). This difference in dialysis withdrawal between different ethnicities is unclear, though highlights the role of social and cultural values in decision to withdraw or continue dialysis (10, 11). One of the reasons for the increase of likelihood of DW in whites may be related to more liberal values, as religious,

societal and cultural beliefs play an influencing role in deciding continuation or withdrawal of dialysis (10, 44, 45). The difference may also be more pronounced in a geographical setting with historical issues, such as in the US, where non-white race lacks trust in health care and physicians' advice of dialysis withholding, due to inequality in health care, leading to continuation of dialysis as compared to whites (46).

The association between dialysis withdrawal and gender is inconsistent and inconclusive. Gessert et. al. has shown that women are more likely to withdraw from dialysis than men, a higher DW rate in women vs men (26.3% vs. 23.0%, $p < 0.001$) (36). However, Seshasai et al. (2016) found males had a high withdrawal rate than females (9). The difference in studies may be related to gender inequality in treatment and management decision-making (10, 47). Gender bias in clinical-decision making is still prevalent in many under developed regions and low socio economic areas (10, 47). In some religions, cultures, societies, race and ethnicities, women are less privileged than men and have less access to expensive, quality health care, such as renal dialysis and transplantation (10, 47).

The area of residence is also associated with dialysis withdrawal. Residents of small towns and villages have a higher rate of DW compared to those living in larger towns and cities (26.9% vs. 24.3%, $p < 0.001$) (10, 36). Authors have also shown that marriage status such as divorced or widowed and/or living in nursing homes is one of the predictors of DW (18, 48). However, Birmele et al. (2004) found that living alone, or with family or spouse is not a significant predictor of withdrawal (13). However, its worth noting that this study has a small subsample size (n=40) in DW group. Similarly, authors have shown that single, married, or divorced was not associated with dialysis withdrawal, though the association was significant in unadjusted analysis (17, 18). Fissell et al. (2005) found that living in the nursing home was

significantly associated in adjusted and non-adjusted models, and less than 12 years of education was an insignificant factor in both the models (18). The same study also found employment is a significant factor in dialysis withdrawal (18). The authors pointed out that patients of lower socio economic status such as less education and lower employment status are underprivileged members of the society who may lack access to good quality health care, communication, transport and community support system that facilitates them to continue the treatment which requires frequent visitation (3-4 times for conventional HD) to the dialysis centre (18, 48).

2.2.2 Renal Disease

The primary aetiology of renal disease is also associated with DW. Patients with renal failure caused by hypertensive renal disease have higher risk of DW than those with glomerulonephritis. Ellwood et al. (2013) found diabetes-induced ESRD and renovascular disease were associated with increased rate of DW (HR= 1.58 [95% CI 1.37– 1.82] and HR= 1.26 [95% CI 1.06–1.49], respectively) (11). However, Birmele et al. (2004) found causes of CKD such as glomerulopathy, diabetic, interstitial and vascular nephropathy and polycystic kidney disease were not associated with DW (13). Furthermore, another study showed that type 1 diabetes was associated with DW but type 2 diabetes and glomerulonephritis, amyloidosis, polycystic kidney disease and nephrosclerosis were not associated (49). These insignificant findings may be attributed to the small subsample of DW patients, as many of the subgroup of aforementioned renal diseases have only 1 to 5 patients (49).

2.2.3 Health Behaviour

Behaviour risk factors such as smoking, substance abuse and alcohol dependence, and BMI are associated with DW. Seshasai et al. (2016) showed that smoking and alcohol use were

associated with DW in hemodialysis group (HR=1.34 [95% CI 1.01-1.78]) (9). Similarly, Fissell et al. (2005) showed that patients who have alcohol dependence have higher odds of DW in unadjusted analysis, but the same risk factor was insignificant in the adjusted analysis. (18).

Patients having a low BMI may have malnutrition and poor health status, increasing the odds of DW, due to the worsening of comorbidities and physical deteriorating condition associated with continuation of dialysis. Having a BMI higher than 18.5 kg/m (HR= 1.37[95% CI 1.16–1.61]) is associated with increased rates of DW (11). However, categorization of BMI into underweight (<18.5), healthy (18.5-25), overweight (>25-30) and obese (>30) were not associated with DW of PD patients (14). The difference in the relationship between DW and BMI may be attributed to type of dialysis with withdrawal from PD less dependent on BMI as compared to HD.

2.2.4 Laboratory Indicators

Laboratory values such as serum albumin, creatinine, phosphorus/phosphate and hemoglobin are associated with DW. Hazama et al. (2014) found hemoglobin and albumin were associated with PD withdrawal, but creatinine and uric acid were not associated (15). Excretion of peritoneal albumin is significantly associated with cardiac diseases, resulting in dialysis withdrawal (50-52). Another study showed that serum creatinine and phosphate were associated with withdrawal, but serum potassium was not associated (17).

The relationship between serum phosphate and dialysis withdrawal, highlights the importance of dietary control of phosphorus and use of phosphate-binder medication during dialysis, as these preventive measures decreases DW (17). Serum creatinine was associated with dialysis withdrawal (17, 11, 53).

2.2.5 Comorbidities

Authors have found that comorbidities such as dementia, diabetes, cerebrovascular diseases and malignancy are associated with dialysis withdrawal. Addition of comorbidities and their combination are also positively associated with DW (10). Patients with chronic conditions such as cancer, dementia, diabetes, hypertension and cachexia are more likely to withdraw than those with acute conditions such as stroke, infection, angina and heart failure disease (13). Chronic diseases gradually deteriorate a patient's health status, leading to complications that could cause a cascade of health issues, increase the burden of disease, resulting in the patient's withdrawal from dialysis treatment (42).

Patients with poor health status at the start of dialysis have higher risk of dialysis withdrawal. In addition to a patient' physical health, quality of life measures, especially pain, is found to be a significant predictor to DW. A study has shown a higher withdrawal rate in patients suffering from chronic pain (54). Davison (2012) found that almost half of patients (50%) have significant pain at the time of discontinuation of dialysis (55). However, it is difficult to distinguish and understand the biologic plausibility between pain and depression in relation to dialysis withdrawal (17, 54). Since patients with comorbidities have higher risk of depression, despair, loss of positivism and hopelessness than patients without comorbidities (17, 54), a patient's decision to discontinue the dialysis treatment may be due to depression and not with chronic pain/discomfort (17, 54).

2.2.6 Dialysis Modality and Duration

The relationship between dialysis modality such as hemodialysis (HD), home hemodialysis (HHD) and peritoneal dialysis (PD) and DW is unclear. Mizuno et al. (2011) found

a higher rate of DW in HD patients than that of PD patients (12). Chan et al. (2012) found a negative effect of peritoneal dialysis on dialysis withdrawal in both unadjusted and adjusted models (10). This difference in findings between studies may be explained by the general health status, disease burden and comorbidities at the start of dialysis (13). Peritoneal dialysis is mostly performed at home in patients that have more self control and family support to be able to perform routine dialysis (13). This self control improves patient's confidence, active participation in daily activities, and mental health and wellbeing, perhaps reducing chances of dialysis withdrawal, as compared to in-hospital hemodialysis (10, 13). This finding may be attributed to selection bias and confounding. Patients having high disease burden and comorbidities have higher odds of undergoing HD than PD (13).

The poor mental health status is associated with dialysis withdrawal; and, HD patients have higher rate of dialysis withdrawal than PD (54). However, few authors found insignificant effect of type of dialysis on dialysis withdrawal (13). Ellwood et al. (2013) found patients undergoing hemodialysis have a higher rate of withdrawal as compared to patients in non-withdrawal group, but type of dialysis modality (HD vs PD) was insignificantly associated with DW (11).

The relationship between duration of dialysis and DW is inconclusive, as McDade-Montez (2006) found insignificant association for duration of dialysis (in month) between withdrawal and non-withdrawal group (17). This finding may be attributed to small subsample of dialysis withdrawal group (n=40). Another study showed that duration of dialysis in years was not significantly different between patient who withdrew and continue dialysis (13). Many of the dialysis patients have short survival, and exploration of duration of dialysis in months or number of days may be more appropriate measure as compared to years, selected in the above studies.

2.3 Review Summary and Research Gap

The literature review revealed a scarcity of research on the factors associated with dialysis withdrawal. The findings of the studies are inconsistent and inconclusive. Authors have shown differences in dialysis attrition rates and factors associated with dialysis withdrawal, and the direction and strength of the association for similar factors is also inconsistent. This difference may be due to several reasons. The definition of dialysis withdrawal is not consistent, as authors have used this concept in terms of discontinuation, withholding, death, withdrawal, treatment refusal/ceased, or technique failure (8-11, 14, 17).

The discontinuation was defined as no dialysis treatment within sixty-day period (9). Withdrawal was defined as either withdrawal from treatment, suicide, and accidental death or patient refusal for further treatment or treatment ceased (10). Withholding therapy was defined as stopping or not to start or increase a life sustaining intervention. Few studies have also provided exclusions while defining dialysis withdrawal as excluding patients with return of kidney function (11). Technique failure was defined as discontinuation of peritoneal dialysis for > 6 weeks (17).

Dialysis withdrawal rate and associated factors are dependent on the type of modality such as HD or PD (9, 12, 14, 15, 17, 18, 21). Many of the studies have selected either PD or HD patients but not both, making comparisons and inferences difficult to interpret (9, 12, 17).

Patients with comorbidities, such as diabetes, and heart diseases and other chronic debilitating diseases are associated with dialysis withdrawal (10). Poor general health condition due to comorbidities can further reduce quality of life of the dialysis patients,

resulting in more likelihood of dialysis withdrawal than with patients of otherwise good health condition (13, 20, 21). However, few authors have also shown insignificant effect of diabetes, vascular disease, stroke, cancer, arrhythmia and lung disease. This difference may be explained by number of diseases or comorbidities included in the study and duration, severity and type (10, 23).

Old age, females, whites and having chronic diseases are associated with dialysis withdrawal (10, 11, 20, 21). However, few studies showed that demographic factors are not associated with dialysis withdrawal (13, 18). The geographical setting of the study has also accounted for these differences, as race/ethnicities, preferences and whether to withdraw dialysis are sociodemographic dependent (9-13, 15-21).

Chapter 3

Study Rationale and Research Objectives

3.1 Rationale

Considering the scarcity of literature, a high prevalence of dialysis withdrawal and inconsistent results warrant further exploration of the topic by conducting an original study to identify the factors that can influence a patient's decision to withdraw from dialysis (10-17). The proposed study will provide better understanding of the factors and their association in relation to dialysis withdrawal and if the dialysis modality influences this relationship. This understanding will help the care provider and patients alike to improve the clinical decision-making by identifying patients who are at risk of withdrawal from the treatment. Interventions to influence the modifiable risk factor can be offered to help patients to achieve a better survival outcome.

3.2 Aims and Objectives

The purpose of the study is to perform a retrospective analysis of chronic dialysis patients and their corresponding treatment modalities in relation to factors that determine dialysis withdrawal. The primary objective of the study was to determine the rate of dialysis withdrawal and factors associated with dialysis withdrawal in chronic dialysis patients. The secondary objective of the study was to identify the reasons for dialysis withdrawal.

Chapter 4 Methodology

4.1 Study Design

This retrospective study used structured and unstructured clinical data to extract the relevant information from hospital data sources. The study explored the factors associated with dialysis withdrawal in chronic dialysis patients, within the last five-year period (2012-2017) in Grand River Hospital, a large community hospital with a regional renal program in the region of Waterloo, Ontario, Canada.

4.2 Study Sample

4.2.1 Inclusion criteria

The study cohort included all adult patients (>18 years) who initiated chronic renal dialysis therapy and were registered in the Renal program at Grand River Hospital (GRH), Ontario, from 1st January, 2012 to 30th September, 2017. The dialysis duration of 30 days or more was considered as chronic renal dialysis. It was calculated by the time elapsed from the first date of dialysis either at home or in centre to the last date of dialysis.

4.2.2 Exclusion criteria

The study excluded patients with only one dialysis date or without any terminal event such as withdrawal, death, transplant, or lost to follow up. However, patients having acute

dialysis (< 30 days) and was discharged/recovered or withdrew, but was later enrolled for chronic dialysis (>30 days), was included in the study. For these patients, the first day of starting the chronic dialysis treatment (coded as modality change to "chronic dialysis" in *Nephrocare*™ was counted as the first day of dialysis. In addition, patients who were coded as chronic dialysis patients prior to the study date were excluded, which is to ensure the study cohort is restricted to incident dialysis patients.

4.2.3 Sampling technique

All patients following the selection criteria were consecutively included during the study period. The selection bias was reduced by restrictive selection criteria.

4.3 Study Setting

Grand River Hospital is a regional health centre serving Region of Waterloo and surrounding communities. The renal program in GRH is one of the largest community renal programs in Ontario, providing services to Chronic Kidney Disease patients, residing in Waterloo Region and Wellington County. The GRH renal program has one main hospital (GRH) and 5 satellite sites.

4.4 Ethics Approval

The Tri-Hospital Research Ethics Board (THREB) and the University of Waterloo Human Research Ethics Committee approved the research project (THREB File # 2016-0619) along with the waiver of "the requirement to obtain patient informed consent", approval form attached as appendix A.

4.5 Data Extraction

The data were extracted from *Nephrocare*™ (electronic patient record system for renal patient management) and clinical notes in *ClinicalConnect*™ System which contains lab reports and clinician reports. The person level data were aggregated and de-identified. All Personal Health Information (PHI) protection measures during the data collection were implemented by ensuring appropriate access control to datasets and the crosswalk file. All data was stored only on GRH managed computers on GRH secure network. Each patient was identified by a randomly generated Subject Identification Number (Subject_ID). A crosswalk file containing the mapping between a Subject_ID and a patient's Medical Record Number (MRN) was stored on a secure computer in GRH.

The extracted data were entered in the excel sheet. The automatically extracted data were validated by randomly selecting the participants and comparing variable values with source data hosted in *Nephrocare*® and *ClinicalConnect*™. The missing values from automatically extracted dataset were completed by careful chart review by two graduate students with formal medical training.

4.5.1 Steps of Data Collection

Firstly, the data for the selected variables were extracted from *Nephroport*® and *Nephrocare*® during February 2017 to May 2017. The descriptive analysis was computed for validation and completeness of the data. The second stage was to review each patient's record for validation and completeness from the *Nephrocare*™ during June to October 2017. Each of the

selected variables were recorded in excel by the two graduate students. A number of patients were randomly selected and their medical record were reviewed for validation and quality of data entry by the two students. The third step was to complete the missing values. *ClinicalConnect*™ was used to review clinical notes and patients report files by the three graduate students. Each patient has several clinical notes and assessments summary (reports) and the logic for identifying most relevant reports include the selection of reports near the start of the dialysis, referral letter, nephrologist assessments, discharge reports, and anaesthesiologist reports.

When reviewing clinical notes, if a diagnosis was found in relevant notes, that diagnosis was recorded in dataset, whereas a diagnosis was not explicitly mentioned in any reports, then the complete sentence relevant to diagnosis was recorded. This sentence was later classified into appropriate diagnosis by the two graduate students with medical background. For comorbidities, if there was any report of a diagnosis by the clinician at the start of dialysis, the patient was considered as having the said comorbidity, irrespective of subsequent recovery or improvement in condition of that disease.

4.6 Study Variables

The dependent variable was dialysis withdrawal (DW), which is defined as "elected-dialysis withdrawal: patient voluntarily refused dialysis treatment and withdrew from the dialysis program". Grand River Hospital's protocol for handing DW requires a patient or his/her caregiver to present the request, followed by the nephrologist's consultation and confirmation, and the necessary arrangement for the palliative care services. A patient who failed to come to scheduled dialysis sessions, or lost to follow up is not considered as a DW patient.

The independent variables were:

1) Age was estimated from the birth year till the date of collection of data, in years.
2) Sex was coded as (Male=1/Female=2)
3) Primary Renal Disease was categorized and coded as (Diabetes =1; Renovascular disease = 2; Other = 3; Nephritis = 4, and Unknown = 5).
4) Comorbidity included following diseases and was coded as (Yes=1/No=2). All the comorbidities were diagnosed at the time of dialysis initiation.

   i. Diabetes (Yes=1/No=0)
   ii. Cardiac disease: Included Coronary Artery Disease (CAD), cardiac arrhythmia, cardiac failure, cardiac valvular disease, pericardial disease, cardiomyopathy, and congenital heart disease. It was coded as (Yes=1/No=0)
   iii. Vascular Accident: Included cerebrovascular accident such as stroke.
   iv. Hypertension (Yes=1/No=0)
   v. Malignancy (Yes=1/No=0)
   vi. Malignancy (Yes=1/No=0)
   vii. Depression (Yes=1/No=0)
   viii. Dementia (Yes=1/No=0)
   ix. Bipolar disorder (Yes=1/No=0)

5) Modality: It was defined as the modality used 90 days after the first dialysis: *Hemodialysis (HD) or Peritoneal dialysis (PD)* and was coded as (HD=1/PD=2) (56).

6) Duration of dialysis: It was measured from the first day of chronic dialysis to the last day of dialysis or any terminal event such as withdrawal, death, transplant, or lost to follow up.

4.7 Sample Size

The sample size was calculated based on the work of Peduzzi et al. (1996) (57).

$$N = 10\,\frac{k}{p},$$

where N is the (minimum) required sample size, k is the number of independent variables in the study, and p is the smallest proportion of withdrawal patients in the population. In our study, given $p = 0.10$ (9,10) based on literature and preliminary analysis, and $k = 7$, the minimum required sample size is *N*=700.

Bayesian Information Criterion (BIC) was used to determine the reliability value (the model selected by BIC being the model considered as being closest to the true model of the observed data) with (*N*=723) patients (58). The minimum reliability with (*N*= 723, d=7) in this study was 86%; where d=p (total predictors=14)-p*(maximum predictors to be included, calculated from sample size estimation) (57).

4.8 Data Analysis

All the data were analyzed by using *SAS® studio University Edition*. The descriptive data include means, standard deviations, frequencies, and interquartile ranges where appropriate. The

binary logistic regression was used to assess determinants of DW with duration of dialysis as confounder.

For binary outcome, we are actually regressing the "tendency" of Y=1 (probability of subject withdrawing from dialysis) on X as follows:

$\eta_i = \beta_0 + \beta_1 X_{1i} + \cdots + \beta_k X_{ki}$; Subject $i = 1, \cdots, n;\ k = 14;$

where

$\eta_i = \log\left(\frac{P_i}{1-P_i}\right)$, i.e., the log-odds of i^{th} subject

where,

η = "eta" is the log-odds of patients who withdrew from dialysis.

β_i(i=0, 14) is the fixed regression coefficient denoting the effect of the corresponding predictor for the intercept including age, sex, modality, diabetes, vascular accident, cardiac disease, hypertension, malignancy, lung disease, dementia, depression, bipolar disorder, mental health, primary renal disease, and duration of dialysis**,** respectively. These variables are used as hypothesis variables in the model where the duration of dialysis as controlled variable.

Chapter 5 Results

5.1 Descriptive Results for Chronic Dialysis Population

The sample size of the study was (*N*=723) chronic dialysis patients. The mean age of the sample was 64.86 (±14.89) years with minimum and maximum values of 19 and 94 years, respectively. Majority (54.1%) of the patients were between 40 to 60 years of age. There were 62.6% (*n*=453) males. The most common cause of renal disease in the sample was diabetes (33.6%) and the most common comorbidity was hypertension (94.5%). The mean duration of dialysis was 544.80 days (±486.83) with minimum and maximum values of 30 and 2009 days. Majority of the patients have a duration of dialysis less than one year. The description of the patient characteristics is provided in Table 2 in detail.

5.2 Descriptive statistics for Withdrawal

The results showed that out of (*N*=723) chronic dialysis patients, 9.41% (*n*=68) patients have dialysis withdrawal. Majority of the DW patients were males (66.18%) with a mean age of 71.72 (±13.90) years. The mean duration of dialysis within DW group was 411.88 (±466.06) days. The patient characteristics in dialysis withdrawal group are provided in Table 3

Table 2 Descriptive Summary of Characteristics of Study Sample

Variable	Summary Statistics
Age in years, *n* (%)	
≤ 40	52 (7.2)
41-60	179 (24.8)
61-80	391 (54.1)
>80	101 (14)
Gender *n* (%)	
Males	453 (62.6)
Females	270 (37.3)
Renal Disease *n* (%)	
Diabetes	243 (33.6)
Renovascular	86 (11.9)
Uncertain	128 (17.7)
Nephritis	78 (10.8)
Others	188 (26)
Comorbidities *n* (%)	
Diabetes	461 (63.8)
Infarct	198 (27.4)
Heart Disease	413 (57.1)
Vascular accident	196 (27.1)
Malignancy	228 (31.5)
Lung disease	172 (23.8)
Hypertension	642 (88.8)
Mental health	232 (32.1)
Depression	213 (29.5)
Dementia	40 (5.5)
Bipolar disorder	18 (2.5)
Modality *n* (%)	
HD	592 (81.9)
PD	131 (18.1)
Duration of Dialysis in years *n* (%)	
≤1	341 (47.2)
≤2	159 (22)
≤3	108 (14.9)
≤4	70 (9.7)
>4	45 (6.2)

Table 3 Descriptive Summary Characteristics in Dialysis Withdrawal Group

Variable	Summary Statistics
Age in years, *n* (%)	
≤ 40	3 (4.4)
40-60	179 (13.2)
61-80	34 (50)
>80	22 (32.4)
Gender *n* (%)	
Males	45 (66.2)
Females	23 (33.8)
Renal Disease *n* (%)	
Diabetes	21 (30.9)
Renovascular	10 (14.7)
Others	16 (23.5)
Uncertain	14 (20.6)
Nephritis	7 (10.3)
Comorbidities *n* (%)	
Diabetes	41 (60.3)
Infarct	23 (33.8)
Heart Disease	48 (70.6)
Vascular accident	26 (38.2)
Malignancy	27 (39.7)
Lung disease	22 (32.4)
Hypertension	65 (95.6)
Mental health	25 (36.8)
Depression	19 (27.9)
Dementia	9 (13.2)
Bipolar disorder	2 (2.9)
Modality *n* (%)	
HD	59 (86.8),
PD	9 (13.2)
Duration of Dialysis in years *n* (%)	
≤1	41 (60.3)
≤2	12 (22.1)
≤3	4 (5.9)
≤4	3 (4.4)
>4	5 (7.4)

5.3 Reasons for Dialysis Withdrawal

The results showed that the most common reason of dialysis withdrawal was non specific cause (51.47%), followed by psychosocial (23.5%) and palliative treatment (10.29%). The reasons for dialysis withdrawal are provided in Table 4 Reasons for Dialysis Withdrawal.

Table 4 Reasons for Dialysis Withdrawal

Reason	n (%)
Psychosocial	16 (23.5)
Cancer	7 (10.29)
Palliative	4 (5.88)
Heart disease	2 (2.94)
Pain	1 (1.47)
Chronic illness	1 (1.47)
Infection	1 (1.47)
COPD	1 (1.47)
Others: Non specific	35 (51.47)

Note. COPD= Chronic Obstructive Lung Disease

5.4 Logistic Regression Results

5.4.1 Individual Model

The logistic regression was performed for each predictor and confounder (duration of dialysis) with dialysis withdrawal to identify significant predictors that can be included in the final logistic regression models. For this approach, p value (level of significance) of 0.2 was considered as significant. The results showed that all predictors were significantly associated with dialysis withdrawal except for sex, kidney disease, diabetes, depression and bipolar disorder. The individual predictors and coefficients (β) are provided in Table 5.

5.4.2 Combined Models

For data analysis seven logistic regression models (Model A to G) were developed using different predictors and confounder. These models were developed to explore the associations between different set of predictors with dialysis withdrawal and to identify the model that can comment on the association between predictors and dialysis withdrawal based on literature, clinical relevance and statistical significance.

Table 5 Logistic Regression Results for Individual Predictors

Variables	β (coefficient); p values
Age	0.040; 0.0002*
Sex	-0.072; 0.59
Kidney Disease	Nephritis (0.109; 0.675), diabetes(-0.086; 0.700), other (-0.216; 0.381), renovascular disease (0.231; 0.434).
Diabetes	0.045; 0.730
Hypertension	-0.872; 0.017*
Malignancy	-0.220; 0.095*
Lung Disease	-0.237; 0.085*
Depression	0.012; 0.931
Dementia	-0.688; 0.0005*
Bipolar Disorder	-0.058; 0.879
Vascular Accident	-0.338; 0.012*
Modality	0.441; 0.019*
Cardiac Disease	-0.404; 0.002*
Duration of dialysis	-0.0007; 0.017*

Note. *$p < 0.2$ was considered as significant.

Model “A” included all predictors (irrespective of statistical significance) and showed that age, cardiac disease, hypertension and dementia and duration of dialysis as a confounder were significantly associated with dialysis withdrawal, Model “B” included all significant predictors (except mental health component: dementia) and showed that age, hypertension and duration of dialysis (confounder) were significantly associated with dialysis withdrawal. Model “C” included all statistically significant predictors and showed that age, cardiac disease, hypertension, dementia and duration of dialysis (confounder) were significantly associated with dialysis withdrawal.

Model “D” included the most relevant seven clinical predictors (irrespective of significance) and showed that age, hypertension and cardiac disease and duration of dialysis as confounder were significantly associated with dialysis withdrawal. Model “E” included all clinical significant predictors and showed that age, cardiac disease, hypertension and dementia and duration of dialysis (confounder) were significantly associated with dialysis withdrawal. Model “F” as shown in Table 6 was based on BIC (Bayesian Information Criterion) model selection, an algorithmic based selection of model. BIC provides a way to choose among different models with different numbers of variables by BIC scores. For this model, all predictors we included for model selection by BIC and the models with the lower BIC values are preferred. The model including variables of age, duration of dialysis, hypertension and dementia was preferred, based on BIB scores. This finding was similar to all the above models “A-E” except cardiac disease, not identified in BIC model “F”.

Table 6 BIC Model "F"

Obs	CandModel	BIC scores
1	Age HTN	444.722
2	Age DD HTN	445.248
3	Age	445.858
4	Age DD HTN DE	448.589
5	Age DD	448.603

Note. HTN=Hypertension, DD= Duration of dialysis, DE=Dementia

5.5 Selection of Final Model

The results from models "A-F" showed that predictors age, cardiac disease, hypertension and dementia were significantly associated with dialysis withdrawal, with significant influence of duration of dialysis on the above relationship. This finding indicates that the above predictors have a significant influence on dialysis withdrawal, irrespective of the number and type of variables selected within a model. The model parameter SAS outputs of all models "A-G" are provided as Appendix B.

Based on the above models, sample size estimation (maximum number of predictors that can be included in the model) and the clinical and statistical significance of individual variables, model "G" was constructed as final model with age, modality, diabetes, cardiac disease, hypertension and dementia as predictors and duration of dialysis as confounders. To reiterate, that final model "G" was selected based on clinical and statistical significance and model "F" was BIC based model selection. The BIC model selection was in line with the final model,

selecting almost similar set of variables. Hence, supporting the model based on clinical understanding and logic. The logistic regression parameters for individual predictors with confounder and for models “A-G” are provided as Table 7.

Table 7 Logistic Regression parameter estimates for Individual and combined models "A-G"

Variable	Individual: β (coefficient); p values	Model A: β (coefficient); p values	Model B: β (coefficient) ; p values	Model C: β (coefficient) ; p values	Model D: β (coefficient) ; p values	Model E: β (coefficient) ; p values	Model F: β (coefficient) ; p values	Model G: β (coefficient); p values
Age	-0.040; 0.0002*	-0.0349; 0.0031**	-0.0387; 0.0007**	-0.0339; 0.0032**	-0.0397; 0.0004**	-0.0342; 0.0024**	-0.0361; 0.0011**	-0.0342; 0.0024**
Sex	0.072; 0.59	0.0962; 0.7360			0.1524; 0.5850			
Kidney	Nephritis= -0.109; 0.675, diabetes=0.086; 0.700, other= 0.216; 0.381, renovascular disease=-0.231; 0.434;	Nephritis= -0.0790; 0.8801. diabetes=0.2192; 0.6708 other= 0.3287; 0.5221 renovascular disease=0.3146; 0.5746						
Diabetes	-0.045; 0.730	-0.4223; 0.2104			-0.3654; 0.1861	-0.4161; 0.1359		-0.4161; 0.1359
Cardiac	0.404; 0.002*	0.7368; 0.0332**	0.6149; 0.0659	0.6843; 0.0428**	0.5802; 0.0308**	0.6530; 0.0166**		0.6530; 0.0166**
Vascular	0.338; 0.012*	0.3897; 0.1776	0.4516; 0.1066	0.3710; 0.1940				
Hypert.	0.872; 0.017*	1.6948; 0.0252**	1.6022; 0.0309**	1.5346, 0.0386**	1.8081; 0.0154**	1.7424; 0.0196**	1.7109; 0.0199**	1.7424; 0.0196**
Lung	0.237; 0.085*	-0.1748; 0.6282	-0.2035; 0.5649	-0.2129; 0.5490				

Cancer	0.220; 0.095*	0.3106; 0.2632	0.3399; 0.2115	0.3398. 0.2145				
Dementia	0.688; 0.0005*	1.0002; 0.0219**		0.9646; 0.0239**		1.1125; 0.0087**	0.9782; 0.0188**	1.1125; 0.0087**
Depress.	-0.012; 0.931	-0.1441; 0.6473						
Bipolar	0.058; 0.879	0.8351; 0.3207						
Modality	-0.441; 0.019*	-0.3322; 0.3977	-0.4392; 0.2537	-0.3766; 0.3306	-0.3718; 0.3317	-0.2986; 0.4388		-0.2986; 0.4388
duration	0.0007; 0.017*	0.000915; 0.0058**	0.000885; 0.0067**	0.000934; 0.0043**	0.000783; 0.0150**	0.000841; 0.0092**	0.000795; 0.0135**	0.000841; 0.0092**

Note. Kidney=Kidney Disease, Cardiac=Cardiac Disease, Vascular=Vascular Accident, Cancer=Malignancy, Hypert=Hypertension, Lung=Lung Disease, Depress=Depression, Bipolar=Bipolar Disorder, Duration= Duration of dialysis; *p<0.2, **p<0.05.

5.5.1 Final Model Results and Interpretation

The final model is shown in Table 8 with model estimates and odds ratios of the predictors. The results indicated that cardiac disease [β=0.6530; p=0.016], hypertension [β=1.7421; p=0.019], dementia [β=1.1125; p=0.008] and age [β=0.0342; p=0.002] were significantly associated with dialysis withdrawal. Hemodialysis and diabetes were not associated with dialysis withdrawal. The results also suggested that duration of dialysis [β= - 0.000841; p=0.0092] significantly influence the above relationship between the predictors and dialysis withdrawal.

From the odds ratio estimates shown in the above table, following can be interpreted from the model:

1) The odds of dialysis withdrawal in patients with cardiac disease was 1.921 [95% CI= 1.126-3.278] times vs patients without cardiac disease, with other variables held constant.

2) The odds of dialysis withdrawal in patients with hypertension was 5.711 [95% CI= 1.322-24.676] times vs patients without hypertension, with other variables held constant.

3) The odds of dialysis withdrawal in patients with dementia was 3.042 [95% CI= 1.325-6.983] times vs patients without dementia, with other variables held constant.

4) One-unit increase of duration, decreases the odds of dialysis withdrawal by a factor of 0.999 [95% CI=0.999-1.00], with other variables held constant.

5) One-unit increase of age, increases the odds of dialysis withdrawal by a factor of 1.035 [95% CI=1.012 – 1.058] with other variables held constant.

Table 8 Final Logistic Regression Model

Parameter	β	SE β	p	AOR	95% CI AOR
Intercept	-6.2350	1.1468	<.0001		
Duration of dialysis	-0.00084	0.000323	0.0092	0.999	0.999 - 1.00
Modality HD vs PD (Ref)	0.2986	0.3857	0.4388	1.348	0.633 – 2.870
Age	0.0342	0.0113	0.0024	1.035	1.012 – 1.058
Diabetes Yes vs No(Ref)	-0.4161	0.2790	0.1359	0.660	0.382 – 1.140
Cardiac Disease Yes vs No(Ref)	0.6530	0.2725	0.0166	1.921	1.126 – 3.278
Hypertension Yes vs No(Ref)	1.7424	0.7467	0.0196	5.711	1.322 – 24.676
Dementia Yes vs No(Ref)	1.1125	0.4240	0.0087	3.042	1.325 – 6.983

Note. *B*=Estimate, *SE B*=Standard Error of Estimate, *p>0.05 as significant, *AOR*=Adjusted Odds Ratio, *95% CI AOR*= 95% Confidence Interval for Adjusted Odds Ratio, HD=Hemodialysis, PD=Peritoneal dialysis

Chapter: 6 Discussion

Dialysis withdrawal is a common outcome in dialysis patients and authors in previous studies have explored the association with dialysis withdrawal. Despite the higher prevalence of dialysis withdrawal and its significant association with death in ESRD patients, the phenomenon of dialysis withdrawal remains unclear (59). The main reason is the inconsistency in defining dialysis withdrawal and scarcity of available literature (59). Authors have used different definitions to define dialysis withdrawal such as either withholding of dialysis, death, any reason for discontinuation, treatment refusal by patients and caregivers, or multiple combinations of these reasons. This study defined dialysis withdrawal as "patient refused further treatment or voluntary withdrawal from the dialysis program confirmed by patient consultation with nephrologist and coordinator".

The study results showed that only 9.41% (*n*=68) patients have dialysis withdrawal in the Regional Renal Program at the Grand River Hospital. The most common reason for dialysis withdrawal was psychosocial, followed by cancer. The study results also indicated that cardiac disease, hypertension, dementia and age were significantly associated with dialysis withdrawal, with significant influence of duration of dialysis (as a confounder) on the above relationship.

6.1 Dialysis Withdrawal

In this study, out of (*N*=723) chronic dialysis patients, 9.41% (*n*=68) patients had dialysis withdrawal during the period of this study. Previous studies have shown a DW rate ranging from 8 to 31% (9-12). Seshasai et al. (2016) conducted a retrospective study on (*N*=2840) dialysis

patients in US, found 24.9% of the patients have dialysis withdrawal (9). Mizuno (2011) conducted a retrospective study in Japan and found dialysis attrition was 31% (11). Chan et al. (2012) found incidence dialysis withdrawal of 3.5% and 13.4% for one and five years, respectively (10). The reason for this wide range of reported rate of dialysis withdrawal may be related to the inconsistent definition of dialysis withdrawal used in these studies.

6.2 Factors Associated with Dialysis Withdrawal:

The results in this study showed that cardiac disease [β= 0.6530; p=0.016], hypertension [β= 1.7421; p=0.019], dementia [β=1.1125; p=0.008] and age [β=0.0342; p=0.002] were significantly associated with dialysis withdrawal. Comorbidities such as diabetes, hypertension, cardiac disease are chronic diseases, gradually deteriorate patient health status, leading to complications that initiate a cascade of health issues (42). These health issues increase the burden of disease and lead patients to discontinue dialysis treatment. This study showed that among the selected comorbidities, only cardiac disease, hypertension and dementia can lead to dialysis withdrawal, highlighting the importance of these factors in chronic dialysis population.

Birmele et al. (2004) found dementia was significantly associated with dialysis withdrawal, but other comorbidities including cardiovascular disease were not associated with dialysis withdrawal (13). Ellwood et al. (2013) and Fissell et al. (2005) also found that vascular diseases and coronary artery disease were positively associated with dialysis withdrawal, but congestive heart failure was not associated with dialysis withdrawal (11, 18). The differences between the results in the present study with the above two studies may be attributed to definition of dialysis withdrawal. The present study defines dialysis

withdrawal as “patient-elected withdrawal” vs. dialysis discontinuation due to any reason except for discontinuation of dialysis due to recovery of kidney functions (Ellwood et al. 2013) and unspecified dialysis termination including Do Not Resuscitate (DNR) patients and death (Fissell et al., 2005) (11, 18).

Wetmore et al. (2017) recently conducted a study defining dialysis withdrawal as “patient and family elected discontinuation of dialysis” found that atherosclerotic heart disease (OR, 0.91; 95% CI 0.88-0.95), hypertension (OR, 1.05; 95% CI 1.00-1.10) arrhythmia (OR, 1.25; 95% CI 1.20-1.29) and other cardiac disease (OR, 1.12; 95% CI 1.08-1.16) are more likely to have dialysis withdrawal, similar to the present study (60). However, Wetmore et al. (2017) did not explore mental health component (dementia, depression and bipolar disorder) in contrast to present study (60). Physical health components such as cardiac and vascular disease, diabetes, infection, cerebrovascular disease, stroke, malignancy, and lung disease have been explored by several authors in relation to dialysis withdrawal, but mental health components such as depression/anxiety and dementia have been rarely explored (9-16, 60). Kurella et al. (2006) found dementia was associated with increased risk of death and dialysis withdrawal (61). However, definition of dialysis withdrawal was not clear in the above study.

Mental health conditions such as depression have been associated with poor psychosocial outcomes, decrease quality of life, adverse medical outcomes such as worsening of kidney functions and death in ESRD patients (62). Similarly, authors have also found significant association between dementia with comorbidities such as cardiac disease, myocardial infarction, cerebrovascular disease, stroke, diabetes, cancer and quality of life (63-65). This relationship between mental health issues and comorbidities such as diabetes, cardiac disease and chronic

kidney disease is complex (62). Patients with comorbidities have a higher risk of mental health issues than patients without comorbidities (17, 54). Similarly, patients with mental conditions such as depressive symptoms and dementia have higher incidence of comorbidities (62). Because of this bidirectional relationship it is difficult to distinguish and understand the biologic plausibility between the comorbid conditions and mental health issues in relation to dialysis withdrawal. This association between comorbid conditions and quality of life with dementia may be the reason of higher odds of dialysis withdrawal in patients with dementia, as found in the present study.

The present study showed that age was significantly associated with dialysis withdrawal that is increase in age increases the odds of dialysis withdrawal. Authors have shown that older age was associated with higher rate of dialysis withdrawal, similar to our findings (10, 11, 37). Ellwood et al. (2013) found that increasing age was significantly associated with dialysis withdrawal (HR, 1.81; 95% CI 1.75–1.88) (11). Wetmore et al. (2017) define dialysis withdrawal as "patient and family elected discontinuation of dialysis", similar to the present study and showed higher odds of withdrawal in dialysis patients with age > 75 years (OR,1.61; 95% CI 1.54-1.68) (60).

Moreover, the relationship between age and dialysis withdrawal is complex. Older age patients have multiple comorbidities that are difficult to control such as diabetes and hypertension that further debilitates with dialysis, leading to drastic deteriorations in physical and mental health and perhaps resulting in dialysis withdrawal (11, 13, 38). However, older people need more social and emotional support, visiting dialysis centre, meeting nursing staff who provide care for them and with whom they can interact and communicate their problems and fears of the disease and treatment (66, 67). Nursing staff not only help in reducing anxiety

and enhancing adaptability, but also supporting decision making, and providing emotional support and education during dialysis, resulting in promoting the positive attitude to continuation of dialysis within these patients (68).

This study did not find any association between sex, dialysis modality (HD or PD), comorbidities such as diabetes, vascular accident, lung disease, malignancy, depression and bipolar disorder, and cause of kidney disease in different models (models A to G logistic regression models), though many of these variables were significant at individual levels (regression models for each predictor and total duration). Authors have shown inconsistent findings between the above variables such as sex, dialysis modality and comorbidities with dialysis withdrawal. Males have negative association (10, 11), females have positive association (59) and sex have no association with dialysis withdrawal (15, 69).

There were inconsistent findings in studies on the association between type of modality and DW. For instance, PD was found negatively associated (Chan et al., 2012) with dialysis withdrawal; whereas Ellwood et al. (2013) and Birmele et al. (2004) found insignificant influence of modality type on dialysis withdrawal. This study also found no association between modality type and DW similar Ellwood et al (2013) and Birmele et al (2004) findings. The inconsistent study findings may be caused by how the modality type was defined in these studies, as many of the patients on PD will eventually have to switch to HD due to complications.

Authors have reported that diabetes and hypertension as aetiology of ESRD were significantly associated with dialysis withdrawal, in contrast to findings of the present study. Similarly, few studies have indicated that comorbidities such as diabetes,

cerebrovascular disease, COPD and malignancy have been associated with dialysis withdrawal, in contrast to insignificant findings reported in this study (9, 10, 60). There are several reasons for the above difference in findings. Firstly, the study selected several comorbidity predictors to explore these associations. Initial logistic models (model A and B) included all predictors and showed insignificant association, may be because of insufficient sample size (Type II error). A priori sample size calculation revealed that maximum of seven variables should be included in the model to minimize type II error (false negative) in this study. Therefore, the final model did not include variables such as lung disease, malignancy, vascular accident, depression and bipolar disorder, based on clinical and statistical significance and to minimize type II error.

Secondly, dialysis (both HD and PD) have few absolute and relative contraindications including severe cardiovascular instability such as severe hypotension, cardiac insufficiency, arrhythmias, and myocardial infarction, intracranial hemorrhage, advanced stage malignancy, uncontrolled serious diabetes, severe bleeding tendency and severe mental problems. The chronic dialysis patients in this study were expected to have already been screened for the contraindications, such as the severity of these diseases and disorders before starting dialysis. Patients with diabetes, malignancy, dementia, depression, bipolar disorder, stroke, vascular accidents have mild to moderate severity of these diseases, not significant enough for these patients to have dialysis withdrawal in this study. Patients with better health status at the start of dialysis have a lower risk of dialysis withdrawal than patients with poor health status (42).

Thirdly, the predictors were measured at the start of dialysis. Many of these comorbidities are not constant and are dependent on several factors such as duration of disease, severity, control, concomitant comorbidities, and risk factors. This study was not able to measure

these factors, progress and control of these comorbidities due to limitations of retrospective data collection. It may be that patients with diabetes have well controlled blood sugar levels, patients with stroke have mild complications, lung disease patients have mild to moderate COPD, depression patients have been controlled and may be cured by medications, reducing the odds of withdrawal in these patients, in the present study.

Finally, the aforementioned relationship between predictors and dialysis withdrawal is significantly confounded ($p<0.05$) by duration of dialysis. Duration of dialysis may influence relationship between comorbidity and dialysis withdrawal, as chronic diseases gradually deteriorate patient health status over time, leading to complications that initiate a cascade of health issues. These health issues increase the burden of disease and lead patients to discontinue dialysis treatment (42). Wetmore et al. (2017) have shown higher odds of withdrawal in patients with higher duration of dialysis vs lower duration (60). However, the odds of withdrawal in this study was just 0.999 [95% CI 0.999-1.00], (close to 1) and hence not clinically meaningful. The reason may be that most of the patients have lower duration of dialysis, as the analysis was restricted to last 5 years only including incident dialysis patients. Patients with start of dialysis prior to start of the study period and more than 5 years of dialysis were not captured in the study, though patients with more than 5 years of dialysis duration are less frequently observed in clinical practice.

The study also identified reasons of dialysis withdrawal. The most common reason was psychosocial (23.5%), followed by cancer (10.29&), palliative care (5.88%), heart disease (2.44%) and pain, infection, chronic illness and COPD (1.47% for each); while for 51.47% of the patients there was no specific reason. Considering the small sample and number of reasons for dialysis withdrawal, further analysis was not performed in this study. Psychosocial reason as the

most common reason among other physical comorbidities such as COPD, infection and chronic illness supplements the study findings in regards to importance of mental health disorders such as dementia vs. physical comorbidities such as malignancy, lung disease and vascular accidents in dialysis withdrawal.

DeVelasco & Dinwiddie (1998) found that one of the common reason for dialysis withdrawal was dementia (70). In addition, societal reasons also have significant influence related dialysis withdrawal (46). Workeneh et al. (2015) found lack of support as one of the main reasons for dialysis withdrawal (16%) (14). However, Cohen et al. (2000) found common reasons for dialysis withdrawal include chronic disease deterioration, acute intercurrent disorder, technical problems of dialysis and failure to thrive (71). The difference in findings in this study may be attributed to small sub sample of dialysis withdrawal and because of > 50% of the dialysis withdrawal patients with no specific cause. Future research is needed to identify the patient-reported reasons for dialysis withdrawal and the factors related to these reasons, to make further inferences.

6.3 Strengths

1) The strengths of the current study include the exploration of a large sample data spanning, last five years and a priori calculated sample size to minimize type II errors.

2) Validity of the data from multiple data sources including *Nephrocare™* and *ClinicalConnect™*. Furthermore, the extracted data was validated by two graduate students separately and by preliminary descriptive analysis.

3) Strict inclusion criteria to reduce selection bias, only including incidental chronic dialysis patients.

4) Clearly defined "withdrawal" as patients-elected dialysis withdrawal, conformed to GRH withdrawal protocol, not include those patients stopped treatment because of a return of kidney function, nor withholding treatment due to imminent death.

5) Consecutive sampling, all participants following the selection criteria within the study period were included, improves the generalizability of the sample.

6.4 Limitations

1. The main weakness of the study is the retrospective study design, which depends entirely on the quality and completeness of the patient records. The quality of the dataset for this study was also dependent on the data quality of clinician notes and data entry of the electronic patient record systems. However, careful review of randomly selected patient records provided limited level of assessment of the accuracy between the extracted data with source system of patient records.

2. Another limitation of a retrospective study was the limitation on variable section for the study. Not all comorbid conditions were recorded reliably in the patient chart, although most of the relevant variables identified in the literature review were documented in *Nephrocare*® by the renal coordinators. The most problematic variables in documentation, are the psychosocial factors such as, depression, income and quality of life, travel distances and lab values.

3. The study wasn't able to explore the relation between financial burden, beliefs, cultural and personal and to the decision to withdrawal the treatment either by family or individual. These topics were beyond the scope of the current study yet are highly relevant for determining the factors that influence DW.

4. Being a single center study the generalizability of the study was limited, but consecutive sampling was performed to make a sample better representation of the target population.

5. Selection and misclassification bias was common in retrospective studies. However, stringent inclusion and exclusion criteria for chronic dialysis patients were applied and clear and measurable outcome were defined, especially the withdrawal definition, which reduced selection and misclassification bias, respectively.

6.5 Advancement of Knowledge and Application in Practice: Implications of the Study

The study showed a low rate of dialysis withdrawal (9.41%) and age, cardiac disease, hypertension and dementia as significant predictors related to dialysis withdrawal among dialysis patients managed by the GRH Renal Program. This finding highlighted that the presence of cardiac disease, hypertension and dementia can increase odds of dialysis withdrawal.

The findings may help developing a screening instrument taking into consideration of the predictors identified in the study such as cardiac disease, hypertension, and dementia. This screening instrument can be used to identify patients with higher risk of dialysis withdrawal at the time of enrolment in chronic dialysis program. This instrument may help clinical decision making and patient care management of patients at risk of dialysis withdrawal by helping them

have a better control of these comorbidities at the dialysis initiation and throughout the entire treatment.

The findings will also help in identifying possible patient specific barriers and issues so early intervention strategies can be developed and applied. Some of these strategies may be frequent patient follow up and treatment, and management care for severity assessment and progression and control of these comorbidities, so as to reduce their risk of dialysis withdrawal in future.

One of the most important finding was identification of mental health component, in particular, dementia as one of the factors associated with dialysis withdrawal. Lack of social support and mental health are known to be one of the main barriers of the continuity of dialysis. These two components are highly interrelated, since lack of social support has a negative influence on mental health. However, due to the limited sample size and the quality of relevant data contained in patient charts, we did not explore these topics in depth.

Most dialysis program screened patients for severe mental health issues prior to the enrollment of the dialysis program, and often will exclude patients with severe mental health conditions. This study identified a need for a modified mental health screening instrument specific for dialysis patients, and the need for continuous monitoring of patients' mental health. Due to its cross-sectional nature, this study was unable to comment on the causal association between mental health and dialysis withdrawal.

The ROC (Receiving Operator Curves) for prediction of DW, while using different set of predictors for models "A-G" were evaluated as shown in appendix B, though predictive modeling was beyond the scope of this thesis. Future steps could include the development of

prediction models for DW, based on different predictors, to identify variables with the highest level of probability and sensitivity and specificity.

6.6 Conclusions

The study showed a low rate of dialysis withdrawal (9.41%) in a cohort (*N*=723) of chronic dialysis patients included in the study. The most common reason for dialysis withdrawal was psychosocial 16 (23.5%) while 35 (51.47%) of the patients didn't have any specific reason for dialysis withdrawal. Age, cardiac disease, hypertension and dementia were associated with dialysis withdrawal, with significant influence of duration of dialysis (as a confounder) on the above relationship in chronic dialysis population. These findings may help in identifying a cohort of patients that are susceptible to dialysis withdrawal at the start of dialysis.

Based on the findings of this study, the following future studies could be designed and conducted:

1. Design and conduct intervention studies focusing on controlling the severity of comorbidities (cardiac disease, hypertension and dementia) by frequent follow up of patients
2. Qualitative study designed to understand the reason for withdrawal including belief, cultural and life style choices on withdrawal
3. Assessment for mental health disorders to better monitor patient's onset and progression of dementia to improve the patient survival outcome.

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APPENDICES

APPENDIX A Research Ethics Approval

UNIVERSITY OF WATERLOO and
TRI-HOSPITAL RESEARCH ETHICS BOARD

GRAND RIVER HOSPITAL

Notification of Ethics Clearance of Application to Conduct Research with Human Participants

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Faculty Supervisor: Helen Chen	**Department:** School of Public Health and Health Systems
Student Investigator: Mahsa Ebad	**Department:** School of Public Health and Health Systems
Student Investigator: Hammad Ali Qazi	**Department:** School of Public Health and Health Systems
Collaborator: Peter Varga	**Department:** Grand River Hospital
Collaborator: Dreck Birtch	**Department:** Grand River Hospital

ORE File #: 22069

Project Title: Patient Decisions regarding dialysis: a review of factors associated with survival and attrition in dialysis patients:

REB File # (THREB): 2016-0619

The Tri-Hospital Research Ethics Board (THREB) and the University of Waterloo ☑ *Human Research Ethics Committee (HREC) /* ☐ *Clinical Research Ethics Committee (CREC) is pleased to inform you the above named study has been reviewed and been found to be ethically acceptable.*

Approval Date: 2/15/17 *(m/d/y)*

Anniversary Date for Renewal: 2/15/18 *(m/d/y)*

THREB and University of Waterloo Research Ethics Committees operate in compliance with their institution's guidelines for research with human participants, the Tri-Council Policy Statement for the Ethical Conduct for Research Involving Humans (TCPS, 2nd edition), International Conference on Harmonization: Good Clinical Practice (ICH-GCP), the Ontario Personal Health Information Protection Act (PHIPA), and the applicable laws and regulations of the province of Ontario. Waterloo Committees are registered with the U.S. Department of Health and Human Services under the Federal Wide Assurance, FWA00021410, and IRB registration number IRB00002419 (HREC) and IRB00007409 (CREC). THREB is registered with the U.S. Department of Health and Human Services under IRB registration number IRB00002344 with Federal Wide Assurance numbers FWA00006013 (Cambridge Memorial Hospital) FWA00005748 (Grand River Hospital) and FWA00002499 (St. Mary's General Hospital). THREB and CREC also comply with the membership requirements as defined in Part C, Division 5 of the Food and Drug Regulations.

Multi-year research must be renewed at least once every 12 months unless a more frequent review has otherwise been specified. Studies will only be renewed if the renewal report is received and approved before the expiry date. Failure to submit renewal reports by the anniversary date will result in the investigators being notified to cease conducting the study and Research Finance being notified the ethics clearance is no longer valid.

Level of review:

☑ *Delegated review*

☐ *THREB committee review meeting date:* _____ *(m/d/y)*

☐ *Waterloo committee review meeting date:* _____ *(m/d/y)*

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

Julie Joza, MPH, Senior Manager, Office of Research Ethics, University of Waterloo
Signed on behalf of: ☑ *HREC Chair* ☐ *CREC Chair*

The above named study is to be conducted in accordance with the submitted application and the most recent approved versions of all supporting materials. Documents reviewed and received ethics clearance for use in the study and/or received for information:

THREB Application for Retrospective Review of Personal Health Information (Medical Charts/Health Records)_Jan 4, 2017

Grand River Hospital Administrative/Institutional Approval of Research Project_Dec 19, 2016

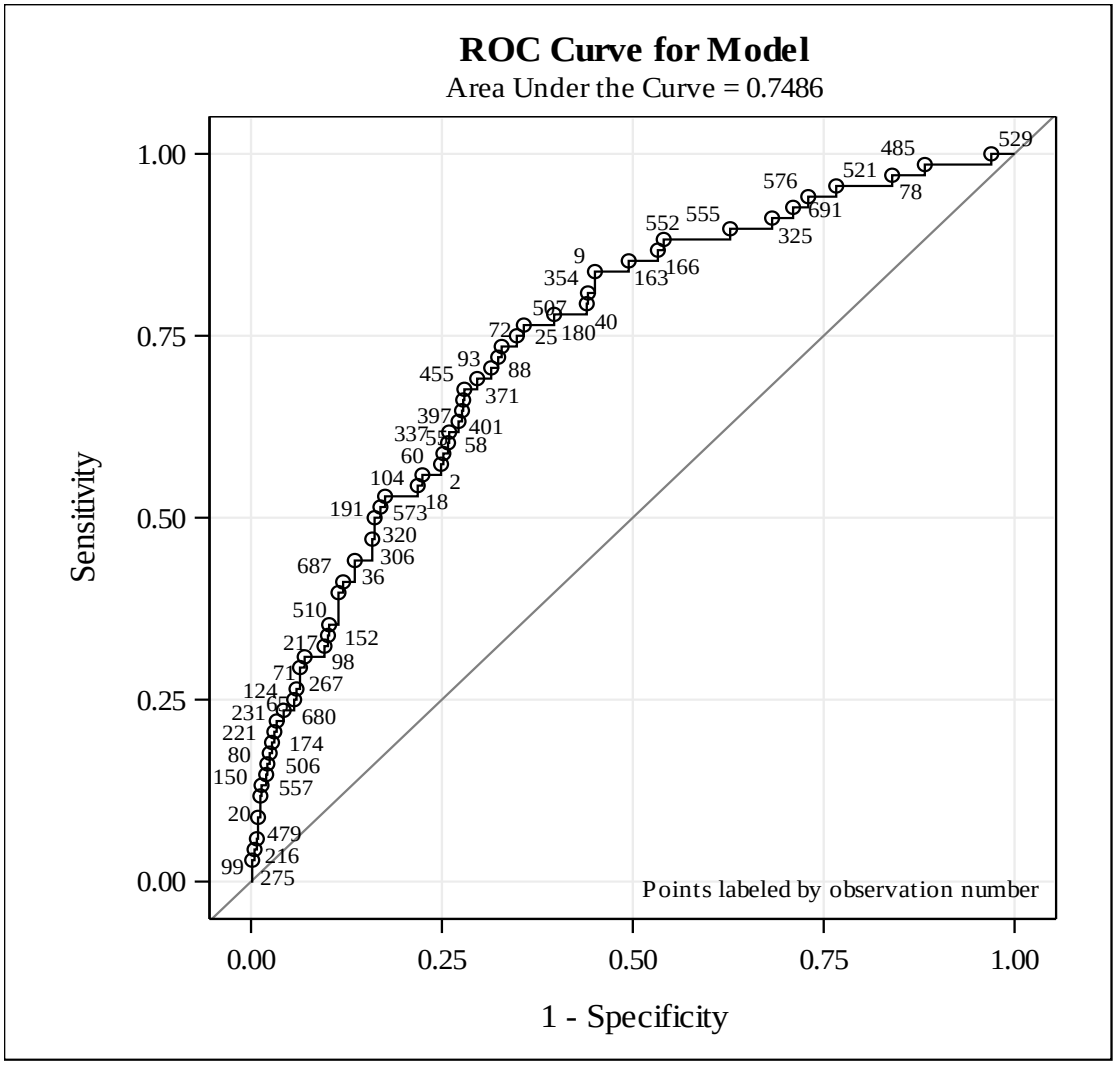
UWaterloo Application (Form 101)_Feb 9, 2017

If there is a contract or data sharing agreement, the study may not commence until those documents have been finalized.

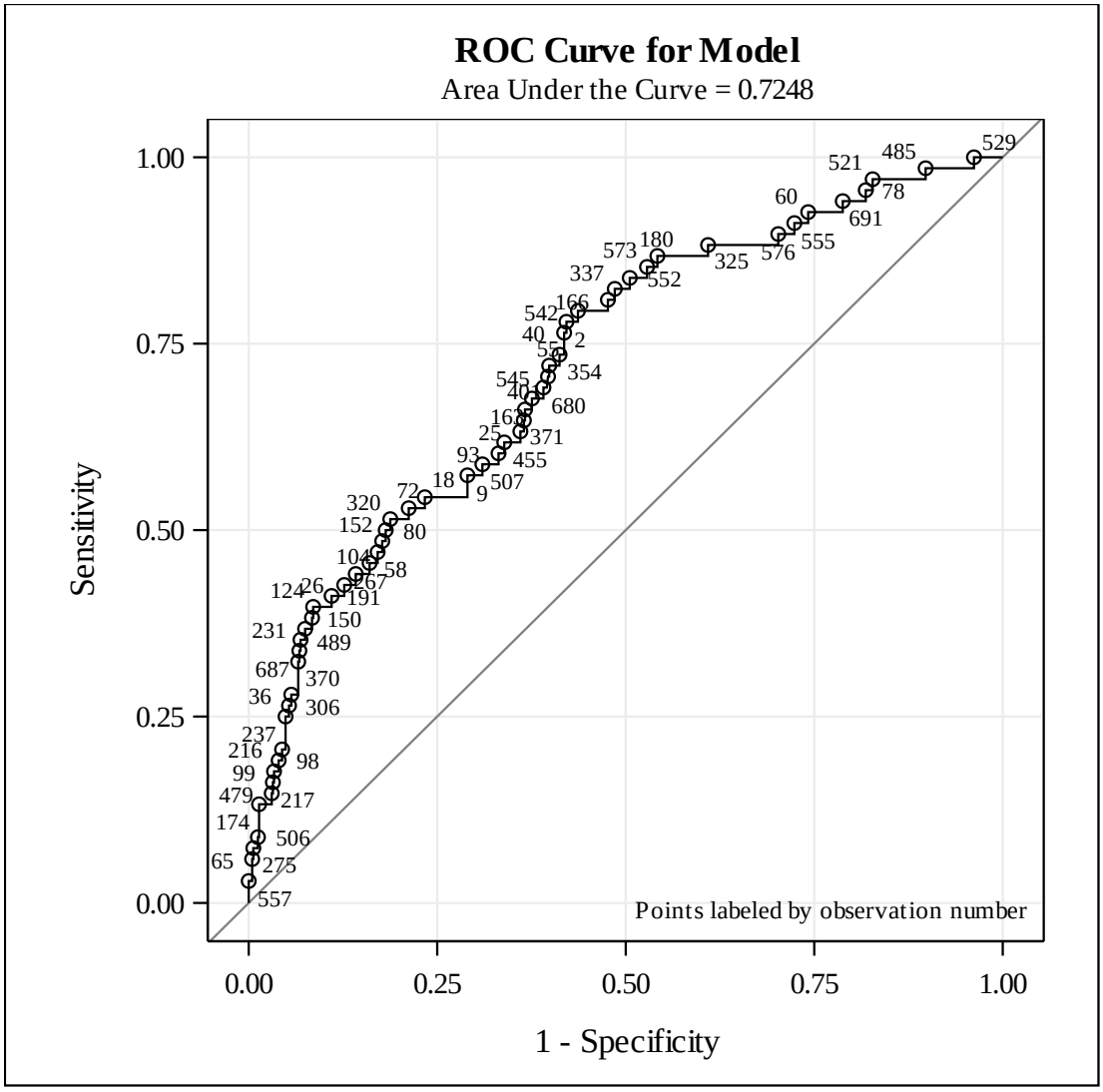
This is an official document. Please retain the original for your files.
You are responsible for obtaining any additional institutional approvals that might be required to complete the study.

APPENDIX B ROC Curve for Models

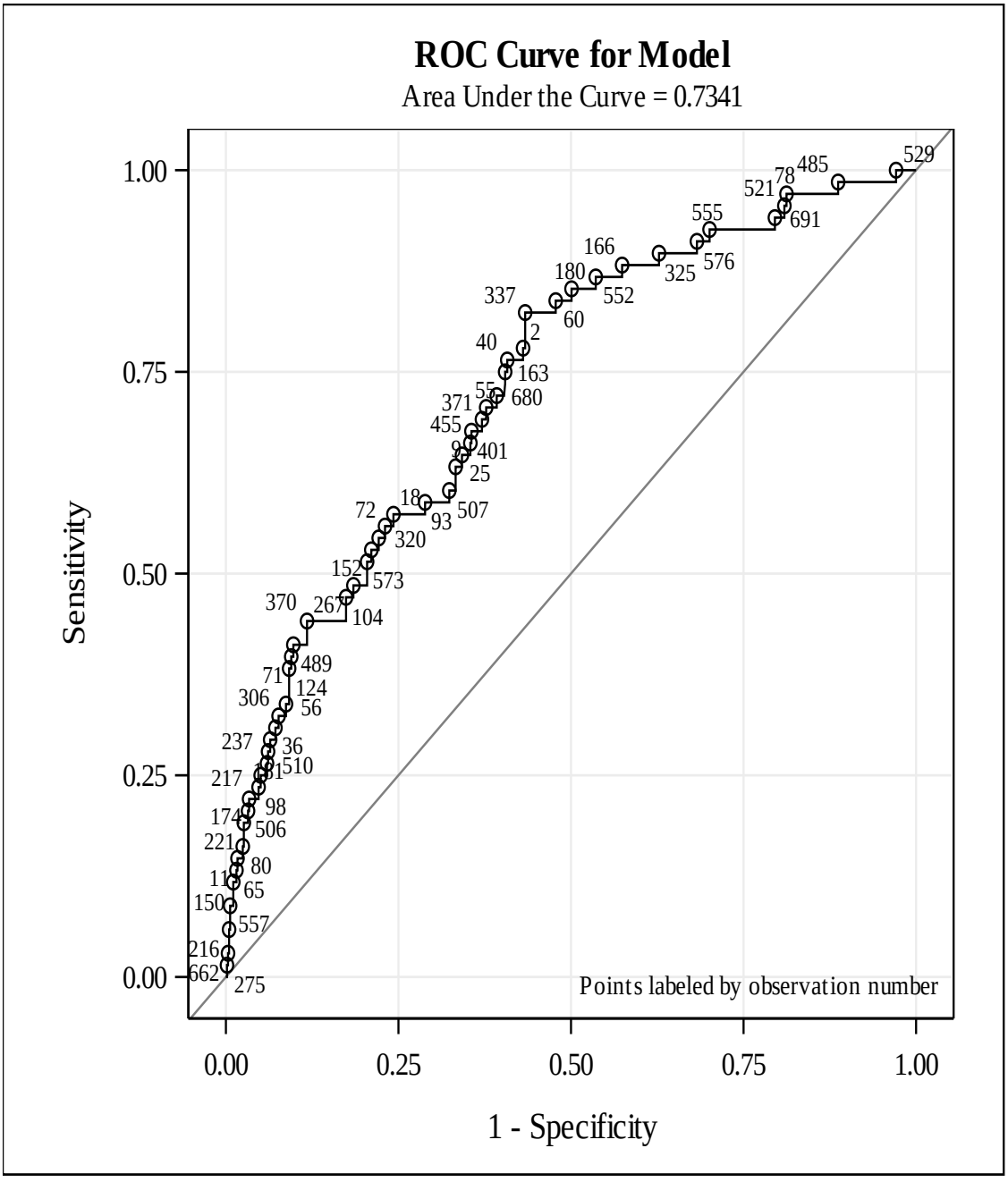
MODEL: A



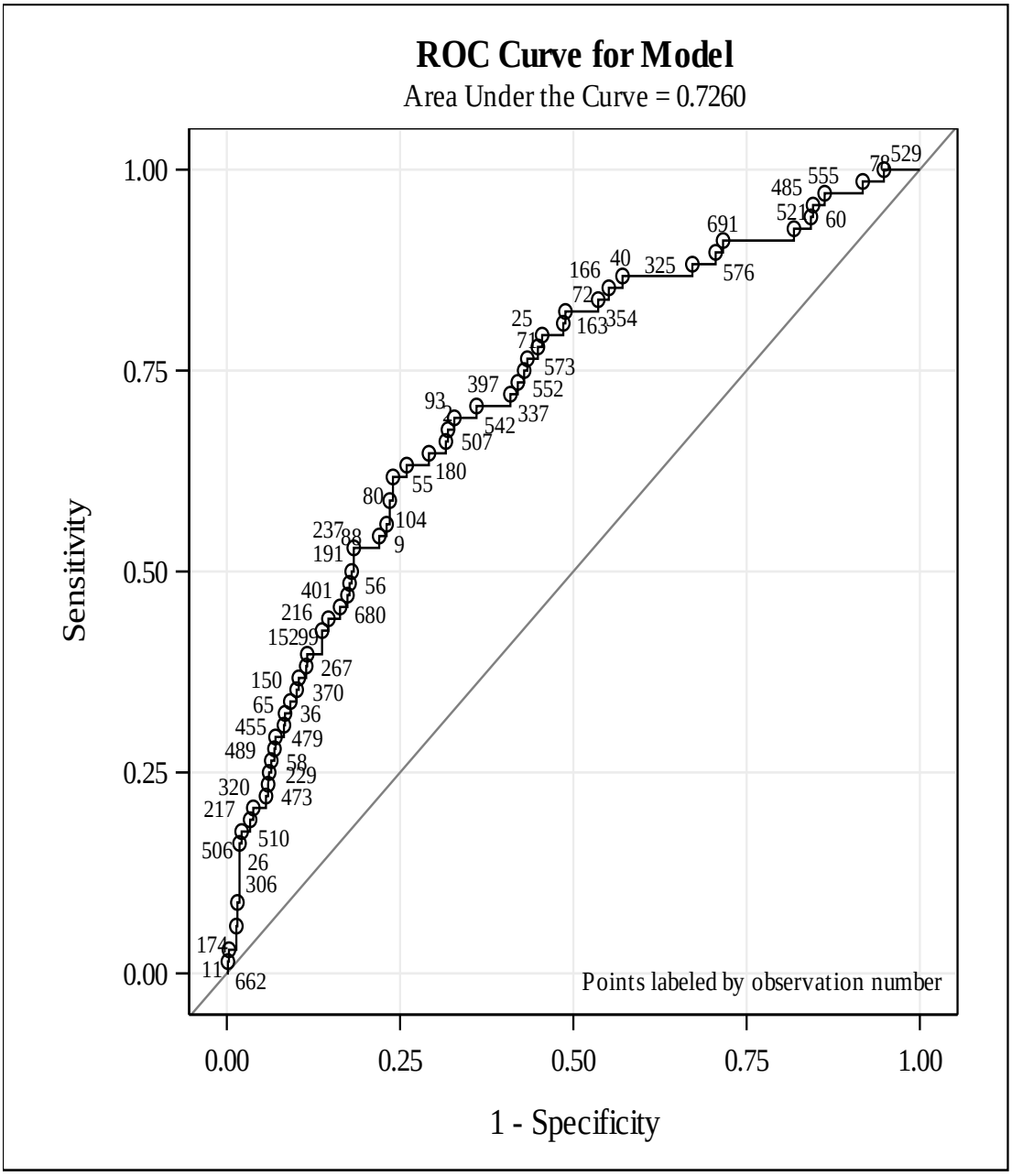
MODEL: B


ROC Curve for Model
Area Under the Curve = 0.7248
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
Points labeled by observation number

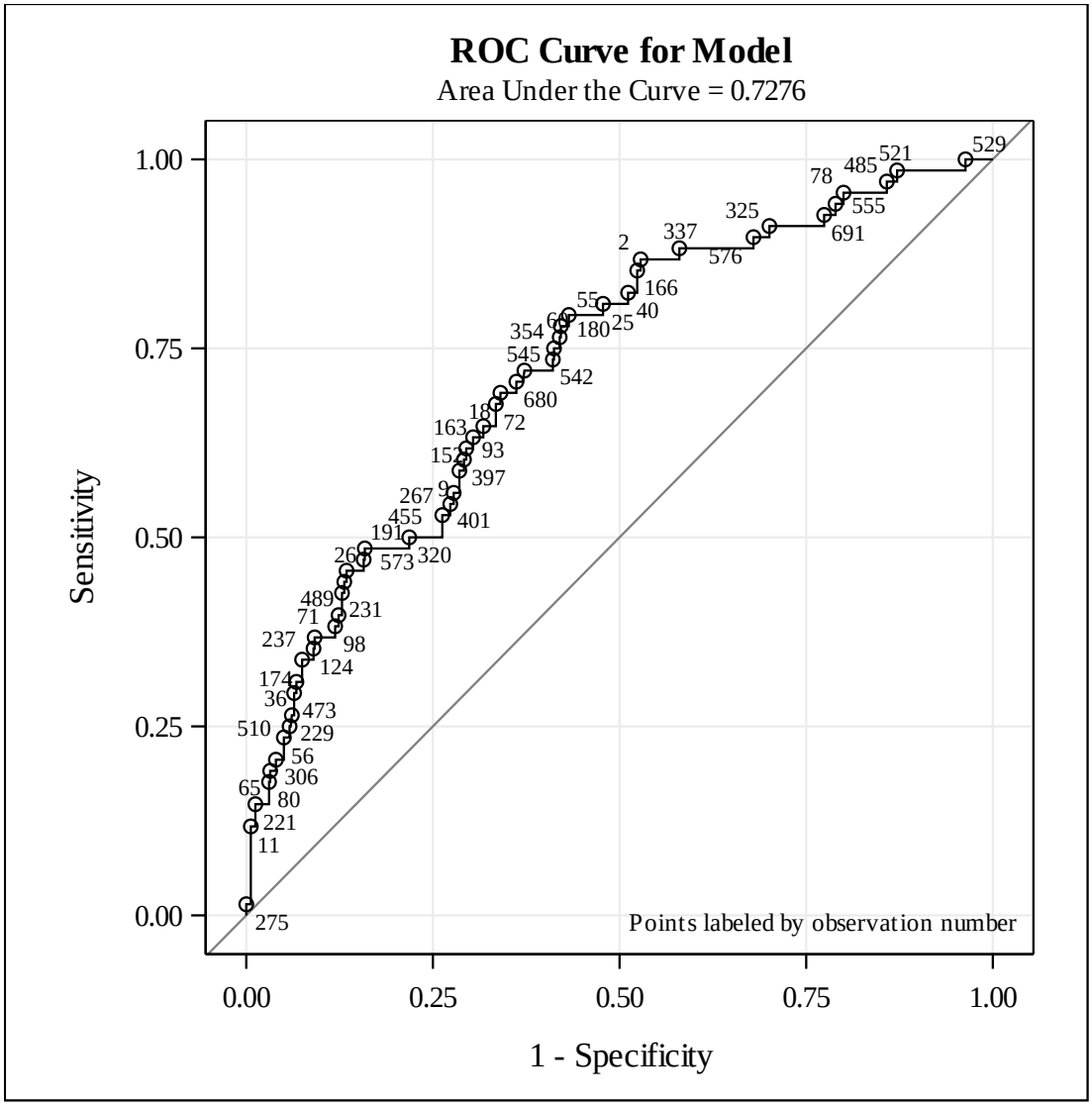
MODEL:C


ROC Curve for Model
Area Under the Curve = 0.7341
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
Points labeled by observation number

MODEL: D


ROC Curve for Model
Area Under the Curve = 0.7260
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
Points labeled by observation number

MODEL: E


ROC Curve for Model
Area Under the Curve = 0.7276
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
Points labeled by observation number
529
521
485
78
555
691
325
337
576
2
166
55
40
25
180
354
545
542
680
72
93
397
401
320
573
191
455
267
231
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98
237
124
174
36
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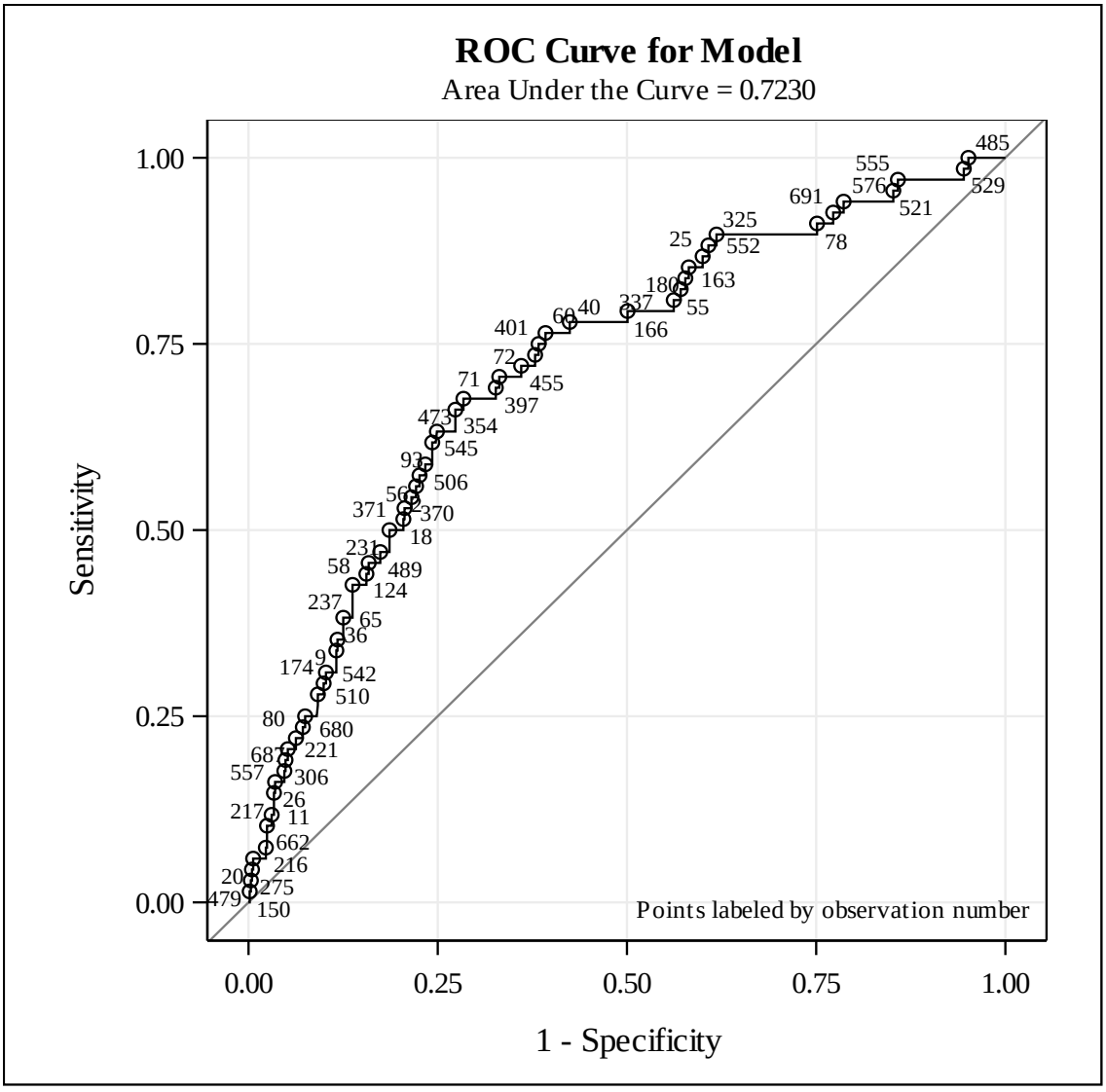
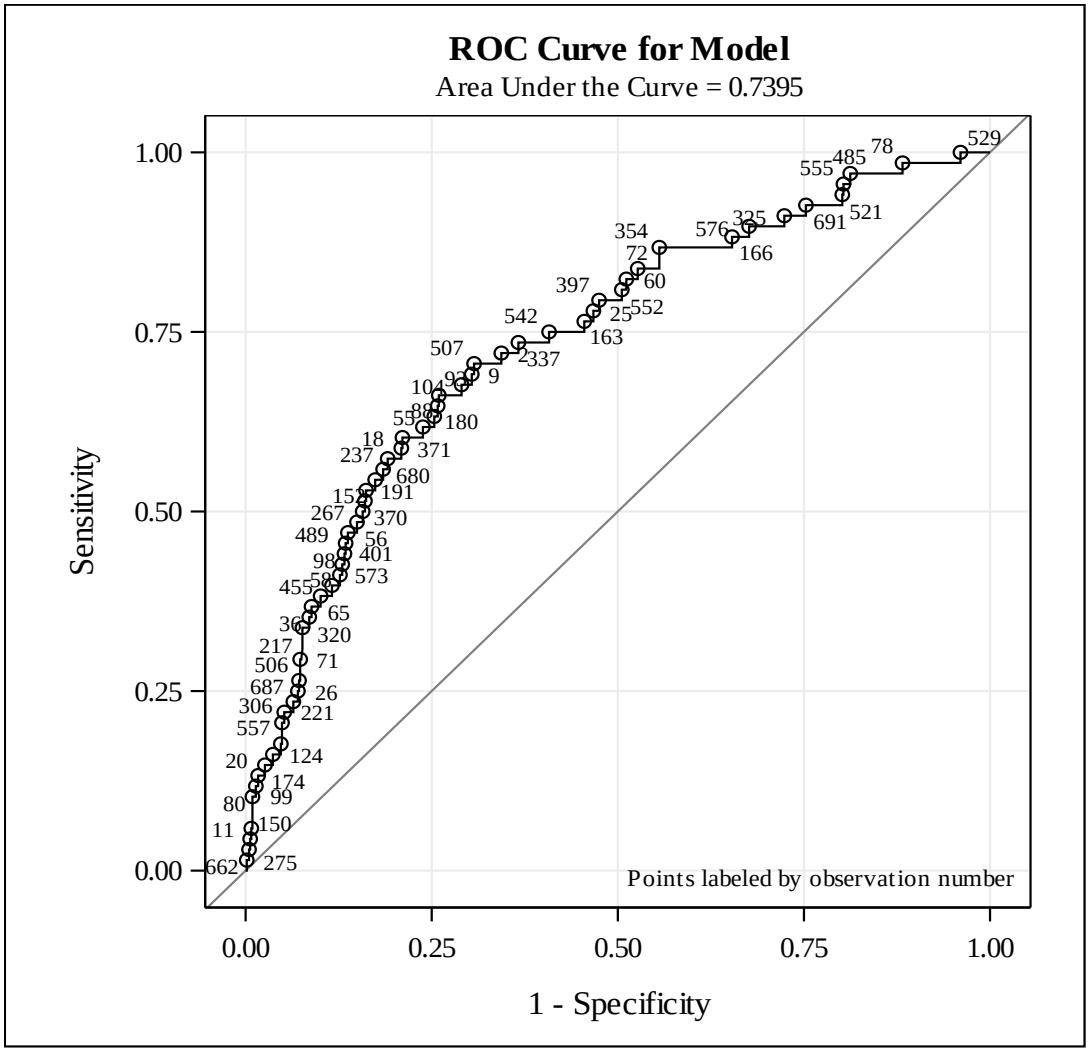
229
56
306
65
80
221
11
275

MODEL: F



MODEL G: FINAL MODEL


ROC Curve for Model
Area Under the Curve = 0.7395
Sensitivity
1 - Specificity
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0.25
0.50
0.75
1.00
Points labeled by observation number
529
78
485
555
521
691
325
576
354
166
72
60
397
552
25
542
163
337
507
9
180
371
18
237
680
191
370
267
56
489
401
573
65
320
71
506
26
687
221
306
557
124
20
174
99
80
150
11
275
662