A COMPARISON OF HOSPITALIZATION OUTCOMES BETWEEN PERITONEAL DIALYSIS AND HOME HEMODIALYSIS PATIENTS IN CANADA

by

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This thesis is dedicated to anyone living with chronic kidney disease. May research continue to make positive change.

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Abstract

Background: Patients using dialysis experience poor health outcomes including high rates of morbidity, mortality, high symptom burden, and frequent and prolonged hospitalizations. In Canada, patients using dialysis are hospitalized 10 times more frequently than the general population. Peritoneal dialysis (PD) is the most common home dialysis option; however, in recent years, home hemodialysis (HHD) has been increasing in use. This is due in part, to some evidence that HHD is associated with better clinical outcomes such as reduced hospitalizations and mortality. However, comparative studies between PD and HHD are limited, and hospitalization outcomes have not been extensively studied.

Objectives: The primary objective was to compare all-cause hospitalization rates, days in hospital, and time to first hospitalization between patients using incident PD or HHD and secondarily to assess if the risk of hospitalization was modified by sex, race, and era of dialysis initiation.

Methods: We conducted a retrospective national cohort study of all adult patients with kidney failure (KF) who initiated home dialysis within 90 days of kidney replacement therapy in Canada between January 1, 2005, to December 31, 2018 (administrative censoring July 1, 2020) using data from the Canadian Organ Replacement Register (CORR) and the Discharge Abstract Database (DAD). Adjusted negative binomial regression modelling was used to compare hospitalization rates and days in hospital between HHD and PD. Time to first hospitalization was modelled using a Fine-Gray subdistribution hazard model. Analyses were stratified across three pre-determined eras (era 1: 2005-2009, era 2: 2010-2014, era 3: 2015-2018) to assess if hospitalization outcomes changed over time.

Results: Our study included 12,708 PD and 715 HHD patients. Those using HHD had a lower hospitalization rate than PD (1.85 per 1000 patient-days vs. 2.44 per 1000 patient-days), incident rate ratio (IRR)= 0.77, 95% confidence interval (CI) 0.70-0.84). Patients on HHD in the second and third eras had 0.66 (95% CI 0.57-0.76) and 0.80 (95% CI 0.67-0.95) lower times risk of admission than PD, respectively. Only the second era for days in hospital was significant with patients on HHD having a 0.58 times lower risk (95% CI 0.37-0.92) of admission compared to PD. Males using HHD had the lowest hospital admission rate (1.72 per 1000 patient-days vs. 2.44 per 1000 patient-days for PD, IRR= 0.72, 95% CI 0.64-0.81) and days in hospital (12.89 days per 1000 patient-days vs. 25.68 days per 1000 patient-days for PD, IRR= 0.67, 95% CI 0.44-1.00). Racial minorities experienced significantly fewer days in hospital compared to the racial majority group (interaction $p < 0.001$).

Conclusion: In this Canadian national cohort study of incident home dialysis patients, those using HHD experienced significantly less hospitalization events than patients using PD. These findings were most pronounced in males and racial minorities.

List of Abbreviations Used

CKD	Chronic kidney disease
KF	Kidney failure
KRT	Kidney replacement therapy
SES	Socioeconomic status
CVD	Cardiovascular disease
QOL	Quality of life
eGFR	Estimated glomerular filtration rate
CORR	Canadian organ replacement register
HD	Hemodialysis
PD	Peritoneal dialysis
HHD	Home hemodialysis
CAPD	Continuous ambulatory peritoneal dialysis (CAPD)
APD	Automated peritoneal dialysis
PPY	Per patient-year
HR	Hazard ratio
RR	Rate ratio
LVH	Left ventricular hypertrophy

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Chapter 1: Introduction

Patients receiving dialysis experience poor health outcomes including high rates of morbidity, mortality, high symptom burden, and frequent and prolonged hospitalizations.[1–4] In Canada, patients treated with dialysis are hospitalized 10 times more frequently than the general population.[5] Home dialysis use, particularly home hemodialysis (HHD), has been on the rise.[6] This is thought to be due to patient preference, greater treatment flexibility and some evidence suggesting improved clinical outcomes and reduced healthcare costs with home dialysis use compared to in-center hemodialysis (HD). In Canada, a "home first" approach is often used,[7] which involves preferentially educating patients on the benefits of home dialysis. However, while home dialysis is beneficial, only a few studies have focused on evaluating and comparing outcomes for patients receiving different home dialysis modalities.

This thesis aimed to investigate the differences in all-cause hospitalization outcomes between incident HHD and peritoneal dialysis (PD) patients across Canada. Most of the comparative outcome studies that exist have focused on mortality as the outcome. Observational research has found that patients receiving HHD have improved survival compared to PD and in-centre HD.[8–10] Studies have also found that HHD is associated with fewer hospitalizations than in-center HD, however, few have compared HHD to PD.[11] There exists a knowledge gap in research investigating differences in hospitalization outcomes between home modalities (PD and HHD) that this thesis aimed to fill. Additionally, recognizing that HHD use has increased substantially in recent years, we also sought to investigate if hospitalization outcomes vary across eras. The rationale for this is that historically, HHD was reserved for the "healthiest patients". However, in recent years with the increasing prevalence of kidney failure (KF), and the prioritization of home dialysis, there has been an increase in older and "sicker" patients being placed on both PD and HHD.

This present thesis is divided into five chapters. The first is an introduction into the topic and aim of the thesis. Chapter two provides a review of the available literature on this topic including an overview of chronic kidney disease (CKD) and KF, types of dialysis,

patient outcomes while using dialysis such as mortality, and hospitalization, as well as the proposed mechanisms underpinning the relationship between home dialysis and hospitalization and a review of the predictors of being hospitalized while using dialysis. Additionally, this chapter summarizes the rationale for this research and the current knowledge gap this thesis aimed to address.

Chapter three contains the study objectives and the statistical methods used in this national retrospective cohort study. This section contains information on the exposure variables, outcome variables, and the selected covariables, originating from the Canadian Organ Replacement Register (CORR) database and, for data on hospitalization, the Discharge Abstract Database (DAD).

Chapter four details the results of the primary analyses as well as the sensitivity analyses. Chapter five concludes this thesis by putting the results into context with the existing literature. This section also provides the strengths and limitations of this study, the implications, and the knowledge translation plan.

Chapter 2: Background

2.1 The Burden of Chronic Kidney Disease

Chronic Kidney Disease (CKD) is defined as decreased kidney function persisting for greater than three months.[1,12–15] It is an increasing global public health problem, and it is estimated that as of 2017 approximately 10% of the world population are living with the disease.[12,16,17] CKD caused 1.2 million deaths globally in 2017.[16] In 2019, CKD was ranked as one of the six leading causes of global disease burden in adults.[18] CKD can range from mild to severe and generally result in gradual loss of kidney function over time, and eventually leads to kidney failure (KF). When someone reaches KF the loss of kidney function is considered irreversible and treatment will be required to survive.[19] In 2019, there were 40,734 Canadians (excluding Quebec) with KF,[20] which is a 33% increase from 2010. It is projected that by 2030, 14.5 million people globally will have KF and require treatment.[21] Treatment for someone with KF is known as kidney replacement therapy (KRT). The gold standard for KRT is a kidney transplant;[22] however, dialysis is commonly used prior to transplant or if a transplant is contraindicated.

KF has multiple causes and regularly co-exists with other medical conditions. As a result, people with KF often have multiple comorbidities. KF is a complex illness, in that many of the comorbidities that cause KF can also be developed due to complications of living with KF, such as diabetes mellitus (DM) and hypertension. The leading cause of KF is DM.[23–25] DM is so prevalent with CKD that it is sometimes referred to as diabetic kidney disease.[26] There are multiple factors related to DM that can cause kidney damage including poor glycemic control, hypertension, obesity, and structural changes to the kidney.[26] In the United States (US), approximately one in three adults with DM have CKD.[27] The incidence of DM related KF is rising faster than the overall incidence of KF.[19] Approximately 38% of patients who start KRT in Canada have DM as their cause of KF.[28] Other leading causes of KF include chronic kidney inflammation (glomerulonephritis or nephritis), polycystic kidney disease, renal vascular disease, and congenital/hereditary renal diseases.[29]

Hypertension is both a significant risk factor and co-morbidity of KF, as well as a major contributor of the progression from CKD to KF.[19,25] Hypertension is variably defined, but many guidelines use a threshold of blood pressure greater than 130/80 mmHg (especially those who have concurrent DM).[30] The prevalence of hypertension was estimated as 95.7% in a cohort study of adult patients living with CKD in the US from 2003 to 2007.[31] Hypertension causes constriction of the blood vessels, including the blood vessels of the kidneys, which impairs kidney function and limits the ability for the kidneys to properly remove waste and excess fluid.[32] Having CKD is also a risk factor for developing hypertension as it affects hormone regulation and salt retention.[33]

Modifiable lifestyle factors that contribute to the development of KF include smoking,[13] alcohol intake, diet (particularly a high sodium diet), and physical activity level.[19,34] Nonmodifiable risk factors include being of older age, having a family history of CKD, and being of Indigenous, Asian, South Asian, Pacific Island, African/Caribbean and/or Hispanic descent.[13] Low socioeconomic status (SES),[12] and obesity[35,36] are other important risk factors. Sex is also a risk factor for KF, [16] with a higher prevalence in females,[37] but greater utilization of KRT in males.[37–39]

KF is an independent risk factor for the development of cardiovascular disease (CVD), which is a major contributor of morbidity and mortality in patients with KF.[40] Evidence supports that as kidney function declines, the risk for CVD increases.[40,41] Many of the risk factors for CKD, such as the lifestyle factors discussed, DM, hypertension, and obesity are also risk factors of CVD,[42] and therefore patients commonly experience both CKD and CVD concurrently. In 2017, 7.6% of cardiovascular deaths were a result of having CKD.[16] Patients with KF are also at risk for other diseases that impact vascular or cardiac health. These include, congestive heart failure, cerebrovascular disease, and peripheral vascular disease,[1,13,19] especially in older adults.[1]

Along with the comorbidities discussed, patients with KF experience many other complications including anemia, cognitive dysfunction, and chronic kidney disease-mineral and bone disorders from changes to mineral metabolism (such as high phosphate

and low calcium), as well as hyperkalemia, which can cause cardiac arrythmia and death.[1] Patients with KF are also immunocompromised from uremia, glucose impairment from diabetes, and malnutrition.[43] Patients with KF experience severe symptom burden, reduced quality of life (QOL) and depression.[2] A study comparing patients with KF to patients with cancer found that those with KF had an average of 17 symptoms compared to 15 symptoms in patients with cancer, and experience similar QOL and symptom burden to those with terminal cancer.[44] Although dialysis can reduce some of symptoms associated with KF, it is still associated with poor health outcomes. Patients using dialysis face high rates of both morbidity and mortality.[3,4] In Canada, only 44.4% of patients using dialysis survive longer than five years.[28]

In addition to its impact on the health of patients, KF is also immensely burdensome on the healthcare system. KRT is extremely resource intensive and expensive with many developed countries devoting 2-3% of their healthcare budgets to treating patients with KF.[12] In Canada, on average, the cost of total care for a patient using dialysis is between $56,000 to $107,000 annually, with the average annual healthcare expenditure of $1.9 billion, which is approximately 1.1% of total healthcare expenditures.[5]

2.2 Dialysis

The primary function of the kidneys is to filter waste such as urea and creatinine, and excess minerals such as sodium and potassium from the blood and excrete it through the urine.[45] They also maintain fluid balance, calcium and phosphate levels, assist in red blood cell production and blood pressure regulation.[19,46] Impaired kidney function causes uremia, which is the build-up of toxins in the blood. Uremia is associated with numerous symptoms including fatigue, neuropathy, cognitive dysfunction, nausea, malnutrition, alterations to taste and smell, insulin resistance, pruritus, serositis, and anemia.[47] Other symptoms of kidney failure include acid-base electrolyte abnormalities, and poor fluid control, resulting in fluid retention and/or high blood pressure.[1]

Dialysis is a life-prolonging treatment that mimics the role of the kidneys by cleaning the blood of toxins and assisting with fluid balance.[46] The number of Canadians requiring

dialysis has increased dramatically in recent years to 23,125 people in 2019, which does not include those who have KF but have not yet initiated KRT or those who have had a kidney transplant.[6] At end of 2019, there were 1,789 kidney transplants performed and 3,299 people on the waitlist for a kidney transplant in Canada. Once dialysis is initiated it generally continues until death or kidney transplant. Dialysis is initiated with the clinical onset of symptoms and/or when the estimated glomerular filtration rate (eGFR), which measures kidney function reduces to less than 5-10 ml/min/1.73 m2.[1,48] Canadian guidelines recommend an "intent-to-defer" approach, where patients with a GFR of less than 15 ml/min/1.73 m2 are to be closely monitored and dialysis is to be initiated when clinical symptoms present or eGFR reaches 6 ml/min/1.73 m2, whichever comes first.[48] Evidence supports that early initiation of dialysis does not improve survival, QOL, or hospital admission rates and given the intensity of chronic dialysis treatment; it is recommended that it should not be initiated until clinically indicated to avoid undue burden to the patient.[48]

Kidney function is monitored using eGFR, which is a measure of the estimate of the rate at which the glomeruli in the kidneys are filtering waste products from the blood. The eGFR is calculated by considering creatinine levels or serum Cystatin C, age, sex, and race,[49] and is generally viewed as the best measure of kidney function.[1] For this thesis, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula.[50] Creatinine levels in the blood are also closely monitored as well as urinalysis to monitor for the presence of proteinuria, specifically albuminuria, which may predispose to kidney function decline.[1] A timely referral for KRT planning is important to ensuring appropriate timing of dialysis initiation or transplant.[1] Clinical practice guidelines recommend that patients be referred at least one year prior to anticipated KRT initiation to allow for appropriate education, as well as other referrals and procedures such as vascular access or transplant teams.

There are two main types of dialysis, hemodialysis (HD) and peritoneal dialysis (PD). HD can be performed in a dialysis center or at home and PD is generally considered a home dialysis therapy. Both HD and PD can be delivered in different ways, with different

terminology throughout the literature. For this proposed thesis, dialysis modality definitions are based on the categories in the Canadian Organ Replacement Register (CORR).[51]

2.2.1 Hemodialysis

HD involves removing blood from the body using a pump and cleaning it with a filter (dialyzer).[19,52] Within the dialyzer are two spaces, one for blood and the other for dialysate. The two spaces are separated by a thin membrane, which allows blood to pass through one side and dialysate through the other. Waste is removed from the blood and passes through the membrane into the dialysate and is removed from the body while the "clean" blood returns to the body.[52] To filter the blood through the machine, vascular access is required. There are three main types of vascular access. The preferred access is a native arteriovenous (AV) fistula, followed by a graft, or lastly a central venous catheter.[53] Optimally, catheters are used temporarily for HD as they are associated with higher risks of infection,[52] however, more often than not they serve as the destination access for hemodialysis, with 84.6% of patients treated with HD using a catheter for initial access in 2019 in Canada.[54] HD can be completed at a hospital, dialysis center, or at home. There are different variations of hemodialysis based on frequency and duration.

Conventional HD is standard hemodialysis that is completed two to four (generally three) times a week for three to six hours at a time (generally four hours).[51] It is primarily completed as an outpatient treatment at a hospital or remote dialysis centre (also referred to as a satellite unit).

Home hemodialysis (HHD) is dialysis that occurs in the patient's home environment and is completed by the patient or a caregiver.[55] Short-daily HD is performed during the day or evening for two to three hours; five to seven days a week.[51,56] Slow-nocturnal HD is another home modality that involves dialyzing for five to six nights a week for six to eight hours.[51,52] Some people complete three to four sessions a week while others complete long-frequent dialysis which is five to seven nocturnal sessions a week.[56]

Despite these definitions, home dialysis does not have to follow a specific schedule and allows for flexibility with timing and duration of treatment.[55]

2.2.2 Peritoneal Dialysis

PD is a home dialysis modality that involves a permanent catheter being placed into the peritoneal cavity within the abdomen and the addition of dialysate to remove waste and excess fluid from the body. As the dialysate sits in the peritoneal cavity, blood and excess water flows through peritoneal membrane and collects in something known as a dwell.[57] The fluid is then drained, and the abdomen is refilled. This process is called an exchange and occurs multiple times a day.[46,52] PD can occur continuously or intermittently. PD has the advantage of preserving residual renal function in patients initiating dialysis for the first time.[58]

Continuous Ambulatory Peritoneal Dialysis (CAPD) involves continuous treatment day and night through the peritoneal catheter. The catheter is connected to bags to manually empty the abdomen and refill with new solution, which is about two to three liters of dialysate.[52] Fluid is contained in the abdominal cavity and is exchanged an average of four times a day in spaced out intervals.[51] Each exchange takes an average of 20-45 minutes and dwells for four to 12 hours depending on the time of day and solution being used.

Automated Peritoneal Dialysis (APD) exchanges are performed during sleep by an automated cycler machine.[46,51] Generally, people connect to the cycler for eight to 10 hours every night, during which, three to five exchanges are performed. Some people complete additional exchanges throughout the day.

2.2.3 Choosing a Dialysis Modality

Dialysis modality choice is primarily up to patient preference unless a medical contraindication exists.[59] Potential contraindications to dialysis include terminal illness, and anatomical issues for PD, such as a uncorrectable hernias and major abdominal surgery with anticipation of significant intra-abdominal scarring or peritoneal

disruption.[57] A prospective cohort study exploring ineligibility for dialysis modalities found that 98% and 87% of patients were deemed medically eligible for in-center HD and PD respectively,[57] leaving the modality decision primarily up to patient choice. Selecting an appropriate modality involves consideration of multiple factors such as distance to a dialysis center, the patient's education and health literacy level, independence, as well as the overall health of the patient and age at treatment initiation, especially if patients are caregiver-dependent.[19,23]

In-center HD remains the most common modality used. HHD was initially introduced in the 1960's and was widely used until the 1970's, but due to the development of PD, increased funding for expansion of in-center or satellite HD facilities, and increased complexity of the patients using dialysis with older age and greater comorbidity, HHD use severely decreased.[60] However, use of HHD has again increased significantly in recent years.[61] This increase is due to a growing body of evidence suggesting that home dialysis may have equivalent or better patient outcomes, be more cost effective than in-center HD,[6,7,62,63] and allow for increased independence for patients. In Canada, there was a 15% increase in home dialysis (HHD and PD) use for the period of 2010 to 2019.[6] Approximately 4-5% of patients now use HHD.[64] PD is still the more common home modality, with about 20% of patients choosing this option.[64] Today in Canada, a "home first" approach is often used,[7] which involves promoting and educating patients on the benefits of home dialysis.

Patients who choose home dialysis tend to have different characteristics than those who choose in-center HD. Patients using home dialysis historically have been younger and healthier,[65] and have tended to have higher health literacy levels, better financial resources, and higher cognitive function and motivation.[7] Patients are more likely to select a home dialysis modality when they have received timely education on treatment options, have appropriate family support, and if their dialysis center is part of a larger facility.[65]

Patients are less likely to choose a home-based modality if they are residing in a rural area, have not received appropriate education of dialysis options, live alone, have a lack of support, or lack space or appropriate housing for dialysis equipment.[65] Racial minorities such as Asian, Black, or Hispanic people have been found to be less likely to utilize home dialysis modalities than White people.[66,67] Racial minority groups are less likely to hold employment or have Medicaid insurance in the US, which can affect access to home dialysis.[66] Pre-dialysis care is a strong predictor of home dialysis use; a study completed by Shen et al. found that both Black and Hispanic patients were less likely to receive a timely nephrology referral and were also less likely to use PD,[66] which has been supported in another study.[68] Barriers specific to HHD include access to clean water, as well as the electricity required to run the machine.[69] These requirements are typically at the patient's expense. HHD also requires a certain level of technological literacy to operate the machine and troubleshoot any potential problems.

In addition to the differences between patients treated with in-center HD or HHD, there are also characteristic differences between patients who choose HHD over PD. Those patients who choose HHD tend to be younger and healthier with less comorbidities than those initiating PD.[55,70] Patients receiving HHD are also more likely to receive a kidney transplant.[71] A Canadian study of 236 patients initiating PD (n=153) or HHD (n=98) at the Toronto General Hospital from 2004 to 2008 found that patient characteristics differ based on home modality selection.[72] At baseline, 57% of patients using PD were male compared to 70% of patients using HHD. Those patients who used HHD were also more likely to be White and significantly younger (PD: 62 ± 16 years, HHD: 46 ± 13 years) than patients using PD. Diabetes and hypertension were leading causes of KF for patients treated with PD, while glomerulonephritis was more common causes of KF for patients treated with HHD. Patients receiving PD also tended to have more comorbidities than those receiving HHD. The authors of this study suggest that nephrologists may be more likely to place younger, "healthier" patients on HHD as it requires extensive education and training and the ability to independently use the dialysis machine. PD requires less training and is not as complex making it potentially more appropriate for older patients or those with several comorbidities. This thought process has also been confirmed in

qualitative research, where 27% of interviewed nephrologists indicated they refer their younger patients with less comorbidities for HHD education.[73]

In recent years, with increasing prevalence of KF, especially in older adults due to an aging population, there has been an increase in older and "sicker" patients being placed on both PD and HHD. Advancements in dialysis technology have also expanded the eligibility of home dialysis, as many machines are now more user-friendly and HHD devices have become more automated resulting in easier use for patients.[59] A study comparing trends in HHD and technique and patient survival in Canada across three eras (1996-2002, 2003-2007, and 2008-2012) found that patients in the more recent eras were older, non-White, had a higher BMI, and had the highest prevalence of diabetes as the cause of KF compared to previous eras.[74]

2.3 Dialysis Modality and Patient Outcomes

Comparative outcome studies between dialysis modalities are important for both patients and care providers to be able to make informed decisions about their treatment options. Comparing mortality and morbidity measures such as hospital admission rates and length of stay can help determine if certain modalities come with greater risk or benefits than others. Comparative outcome studies between PD and HHD are limited, and whether one modality is superior remains uncertain.[5,61,75] Studies to date have often used in-center HD as a comparison group to PD or HHD; however, as discussed, the characteristics between patients receiving in-center HD or HHD are very different. As a result, comparison studies between different dialysis groups often are limited by bias and residual confounding.[55] PD may be a more appropriate comparative group to HHD as both groups are completing dialysis at home and receive education prior to initiating therapy. Nonetheless, the risk of residual confounding is not entirely removed as the majority of dialysis research is observational.

Comparative studies that do exist have often focused on mortality as the outcome. Patients using HHD have been found to have better survival compared to patients using in-center HD.[8,9] However, as Tennankore et al. acknowledges, comparing outcomes

between these two groups may be subject to bias. HHD may appear to be the better modality option based on outcomes; however, those who are ineligible for HHD are typically included in the in-center group.[55] Although scarce, studies comparing survival between HHD and PD have generally found a lower risk of mortality in the HHD group.[11,55,61,65,70] A national Canadian registry study completed using the CORR found that patients treated with incident HHD had 36% lower mortality than those on PD; however, this difference was attenuated in modern eras.[10]

2.3.1 The Burden of Hospitalization in Patients Using Dialysis

While understanding survival differences between dialysis modalities is important, there is evidence to support that patients using dialysis may value QOL over survival.[76] As discussed, patients using dialysis face reduced QOL due to symptom burden and ongoing frequent dialysis treatment, and therefore frequent and lengthy hospitalizations can further reduce QOL. Hospital admissions can indicate the health status of a patient and can be associated with further adverse outcomes, such as repeat admissions, malnutrition, hospital acquired infections, and in-hospital mortality.[77,78]

Dialysis, irrespective of modality is associated with high rates of hospitalization. Patients using dialysis in Canada are hospitalized an average of 1.1 times per patient year (PPY) [5] compared to 0.07 times per PPY in the general population, which is a 16-fold increase.[79] Hospital admissions are higher for US patients using dialysis, (average of 1.58 times PPY), with even higher rates observed in females and White patients.[80] In addition to the impact on patient wellbeing, frequent hospitalizations are expensive and burdensome on the healthcare system. Hospital admissions are the second leading direct cost for patients using dialysis. The average cost of a hospitalization for a patient using dialysis in Canada is $13,634 and approximately $310 million per year for total inpatient costs (excluding Quebec).[5] Therefore, research comparing hospitalization outcomes in patients using dialysis is important for both the potential to reduce healthcare expenditures associated with hospital admissions and improving patient outcomes.

Studies comparing in-center HD to home modalities have found conflicting results. Quinn et al. found no difference in hospitalization rates between patients using PD and in-center HD who were eligible for both therapies.[81] These findings were supported by a 2016 study completed by Oliver et al. who found similar hospitalization rates between patients using incident PD and in-center HD.[82] A 2015 study by Weinhandl et al. found that those using HHD and in-center HD had similar rates of all-cause hospital admission; however, patients using HHD had lower rates of re-admission.[83]

A historical study completed by Murphy et al. comparing the number of days spent in hospital between 822 patients receiving in-center HD or PD across Canadian dialysis centers found conflicting results based on how the exposure was defined and if an intention-to-treat or as treated analysis was used.[84] Hospitalization was compared from dialysis modality at baseline and again from dialysis modality at three months from KRT initiation to account for patients who began on in-center HD and switched to PD. Baseline analysis found that receiving dialysis in-center was associated with greater hospitalizations than PD; however, analysis based on modality at three months found that those receiving in-center had lower rates of hospitalization. In as-treated analyses, where modality switches were accounted for, PD was associated with more hospitalizations at baseline and three months. As this study compared PD to an in-center HD group, there is likely unmeasured confounding as characteristics differ in these populations. It was identified that patients who received in-center HD had more comorbidities than those who were on PD,[84] which is understandable given the historical nature of this study (follow up from 1993-1994), where patients with comorbidities were primarily treated with in-center HD.

No systematic reviews directly comparing hospitalization outcomes between patients using HHD or PD have been conducted to date based on a review of the literature. A 2018 systematic review and meta-analysis of 23 articles comparing mortality and hospitalization in patients using intensive HHD (either short-daily HD or long-nocturnal HD), conventional HD, and PD found that intensive HD was associated with reduced mortality and hospitalization compared to other modalities; however, the overall quality

of evidence was low.[11] Most of the studies included in this systematic review focused on mortality rather than hospitalization outcomes. Comparison of nocturnal HD to conventional HD in three studies resulted in a pooled mean difference of 1.98 less hospital days PPY (95% confidence interval (CI) -2.37, -1.59) and 0.04 less hospital admissions PPY (95% CI -0.46, 0.38) for patients using nocturnal HD compared to in-center HD. There were insufficient studies comparing hospitalization outcomes between HHD and PD to pool results.

There is one previous Canadian national retrospective cohort study investigating hospitalizations in 38,369 patients using dialysis published in 2018.[24] It included all incident chronic users of dialysis in Canada (excluding Manitoba and Quebec) who initiated dialysis between 2005 to 2014. Most patients in this study were on in-center HD. During the study period, there were 112, 374 hospitalizations. The risk of all-cause hospitalization was highest in pediatric patients, followed by patients aged 18-44, with patients aged 65-74 having a reduced risk of hospitalization compared to other age groups. Those who received dialysis at home (regardless of modality) were at a lower risk for all-cause hospitalization (hazard ratio (HR): 0.84, 95% CI 0.79-0.88). Those who received PD had a higher risk of hospitalization within the first seven days of dialysis initiation (HR: 1.27, 95% CI 1.07-1.50) compared to HD, but not after seven days. Although this study was a national Canadian cohort with a large sample size, most analyses looked at dialysis as a whole and did not stratify by modality. Further, HHD was not considered in this study due to the limited number of patients receiving this treatment at the time.

Four observational studies were identified that compared hospitalization outcomes between PD and HHD, all of which found that HHD was associated with lower hospitalization rates and/or less days spent in hospital than PD. A Swedish registry study completed in 2019 used a matched cohort to investigate morbidity (time to first hospital admission, frequency, and number of days in hospital) in patients receiving either incident HHD, in-center HD, and PD from 1991-2012.[71] They found that patients receiving HHD had a significantly lower median annual admission rate of 1.7

(interquartile range (IQR): 0.9-2.8) compared with in-center HD of 2.2 (IQR: 1.1-4.4) and PD of 2.8 (IQR: 1.3-5.3). Annual length of hospital stay was also lowest for patients using HHD (12 days per year [IQR: 6.6-21.4]) compared with in-center HD (14 days per year [IQR: 6.4-33.3]) and PD (20 days per year [IQR: 9.3-41.2]). Patients receiving HHD had the longest time to first admission, with an average of 0.7 years (IQR: 0.2-1.2) compared to 0.3 years (IQR: 0.1-0.8) for in-center HD and 0.4 years (IQR: 0.1-0.9) for PD patients.

The other three studies were completed in the US. The first was a small prospective cohort study of 86 patients completed in Los Angeles from March 2003 to November 2007 that examined hospitalization rates and days in hospital between patients treated with daily HHD (n= 22) or PD (n= 64) and found that those using daily HHD experienced 0.68 admissions PPY and 3.3 days PPY compared to 0.76 admissions PPY and 5.6 days PPY in those using PD.[85] The adjusted risk ratios comparing both admissions and length of stay between HHD and PD patients were not statistically significant. This study was limited by its small sample size, which likely caused lower power to detect significant results and by being confined to one single dialysis center.

The second study was completed in 2015 and used the United States Renal Data System (USRDS) to conduct a propensity score matched retrospective cohort study to compare dialysis-related hospitalizations in patients using PD or daily HHD. Those who received daily HHD had a 0.73 times lower hazard of hospital admission (95% CI 0.67-0.79), with a hospitalization rate of 0.94 PPY, compared to patients using PD who had a rate of 1.36 PPY.[75] Those patients receiving daily HHD spent an average 5.2 days PPY in hospital compared to 9.2 days PPY for those receiving PD. These findings were confirmed with another study completed in 2016 using USRDS records to compare propensity score matched patients using either PD or daily HHD from 2006 to 2010 that found those using HHD had lower hospitalization rates (173.7 versus 199.0 admissions (HR: 0.92, 95% CI 0.89-0.95) and 1,027.2 versus 1,266.9 days per 100 patient-years (RR: 0.81, 95% CI 0.75-0.87) for HHD and PD, respectively).[61] The association was most pronounced when the analysis was restricted to those who initiated home dialysis after more than six

months of KF. Those who began home dialysis (either PD or HHD) at early KF diagnosis had similar hospitalization rates.

Randomized Control Trials (RCTs) with modality comparisons are limited and difficult due to ethical issues around randomizing patients to a specific treatment. Korevaar et al. attempted to conduct an RCT investigating survival and quality of life by randomizing patients to either in-center HD or PD across 38 dialysis centers in the Netherlands from January 1997 to August 2000; however, failed to recruit the minimum number of participants because patients expressed a personal preference for dialysis modality choice.[86] The Frequent Hemodialysis Network (FHN) clinical trials, compared outcomes between different frequencies of weekly dialysis that involved randomizing patients to either three times a week HD for five hours or less sessions, or six times per week for six hours or more[87,88]; however, patients were only randomized to HD frequency and duration, not modality. Furthermore, there were no comparisons with PD in these studies.

2.4 Mechanism Linking Home Dialysis to Hospitalizations

As discussed, KF and dialysis use are associated with frequent hospitalizations. Home dialysis use, specifically HHD has been associated with improved hospitalization outcomes. There are several proposed mechanisms behind this relationship including improved cardiovascular health, reduced anemia, better phosphate control and better nutrition due to a more intensive dialysis regimen.[89,90] Another potential mechanism is that home dialysis (particularly more frequent HHD prescriptions) potentially avoids the two-day interdialytic break that occurs in patients receiving in-center HD, which has been found to be followed by increased rates of hospitalization.[91] Common causes of hospitalizations in patients using dialysis are for cardiovascular reasons, infections, and access related concerns.

2.4.1 Cardiovascular Events

Cardiovascular diseases are the leading cause of death for patients using dialysis and are also a major cause of hospitalization.[92] Patients using HHD have been found to have lower cardiovascular related hospital admissions.[71] Suri et al. found that patients using

HHD had a 0.66 (95% CI 0.58-0.74) times lower hazard of cardiovascular hospital admissions compared to those using PD.[75] Weinhandl et al. also found that compared to PD, those using HHD had lower cardiovascular mortality (HR: 0.81, 95% CI 0.70-0.93), as well as lower risk of cardiovascular related hospital admission (HR 0.85, 95% CI 0.80-0.91).[61]

There are likely multiple factors contributing to these improved cardiovascular outcomes in patients treated with HHD compared to patients treated with conventional HD or PD. One proposed mechanism is left ventricular hypertrophy (LVH), which is defined as increase in the mass of the left ventricle of the heart.[93] LVH is common in patients with KF and is a known risk factor for CVD. Mechanisms for the development of LVH include altered mineral metabolism, anemia, hypertension, and hypervolemia from KF.[94] A Canadian RCT comparing LVH between in-center HD and nocturnal HD, found that that nocturnal HD reduced LVH over a six-month period, compared to patients using in-center HD, which actually had an increase in LVH.[95] Another RCT, which was part of the FHN trials, also identified a reduction in LVH for patients using frequent nocturnal HHD, with a mean decrease of 10.9 grams (95% CI -23.7, 1.8); despite the statistical insignificance of this finding and the wide confidence interval, which is likely due to small sample size, this finding is consistent with the literature.[87] A further FHN trial comparing in-center HD six times per week versus three times per week also found that the those using more frequent dialysis had a greater reduction in LVH.[88]

Other mechanisms for reduced hospitalization in patients using HHD include improved phosphate control and reduced hypertension,[87,88] both of which are risk factors for LVH. A systematic review examining outcomes of patients using daily HD reported that 10 out of 11 studies observed decreases in blood pressure.[96] Other suggestions include better fluid control, better urea clearance and waste removal, and improved mineral metabolism, all of which can affect cardiovascular health. This can be supported by evidence showing that patients using HHD have reduced interdialytic weight gain, suggesting better fluid removal.[88] Fluid overload is a common problem for patients using PD,[97] and has been found to contribute to LVH and hypertension.[98] Additionally, patients using PD often

gain weight at initiation of treatment and tend to have higher levels of blood lipids than patients using HD, which is thought to be from the glucose in the PD dialysate, and therefore potentially increasing the risk of CVD, and subsequent hospitalization.[99,100]

2.4.2 Infection

Infection related hospitalization is common in patients using dialysis.[71,78,101,102] Septicemia and access-related infections are common causes of hospitalization.[78] Lafrance et al. completed a propensity matched cohort study in 2012 and found that 21% and 12% of hospitalizations were contributed to infection for patients using PD and in-center HD, respectively.[102] Those using PD had a 1.52-fold higher hazard of infection related admission compared to those using HD (95% CI 1.34-1.74). Weinhandl et al. found that compared to patients using PD, patients using HHD had lower infection related mortality (HR: 0.71, 95% CI 0.55-0.91), as well as lower rates of infection related hospital admissions (HR: 0.89, 95% CI 0.84-0.94).[61] A study by Suri et al. found that patients using HHD had a 0.81-fold lower hazard ratio (95% CI 0.73-0.90) compared to patients using PD for infection related hospital admission[75]; however, when comparing HHD to in-center HD, those receiving HHD had 1.15 times higher hazard ratio (95% CI 1.04-1.29) for infection related admissions. Another study had similar findings with patients using HHD having a 1.32 times higher hazard of infection related admission compared to in-center HD (95% CI 1.24-1.40).[83]

A potential mechanism as to why patients treated with HHD have more infection-related admissions than those treated with in-center HD is that there may be a higher chance of user error, as patients are completing their own dialysis at home, rather than having a trained professional perform the dialysis in a more sterile hospital environment. Septicemia related hospital admissions are also higher in patients using HHD.[61,75,102] The rationale behind the higher prevalence of septicemia in patients using HHD is thought to be due to the more frequent cannulation (particularly for AV fistula or graft access), increasing the potential for bacteria to enter the blood stream.[75] Suri et al. have postulated that HHD may have higher infection-related admissions than in-centre HD because patients receiving in-center HD have the opportunity to receive intravenous antibiotics

administered during a dialysis session if necessary, while patients using HHD may require admission to administer antibiotics, therefore increasing the rate of infection-related hospitalization.[75]

Reasons contributing to less infection related hospital admissions for HHD compared to PD are similar to the reasons for reduced cardiovascular hospitalizations and include better solute clearance and fluid removal. Patients treated with HHD have been found to fewer uremia-related symptoms.[103] Better dialysis clearance of endogenous toxins through HHD may mitigate the decreased immune function that accompanies uremia and subsequent infection-related hospitalization.[101,104]

2.4.3 Access Complications

As previously described, HD requires access to the bloodstream. Patients using HHD face frequent access complications. Dialysis access related infections (including peritonitis) have been found to be lower in patients using HHD compared to PD[61]; however, higher in HHD compared to in-center HD.[75] Compared to in-center HD, patients using HHD have been found to have greater access failures and procedures.[87,88] It is thought the reasons for this is the increase in use of access due to increased dialysis compared to conventional HD. Patients using HHD must undergo significant patient education. Although PD also requires education, the technique for PD is not as complex. HHD requires self-cannulation, and many patients use AV fistulas. A Canadian study of 202 patients treated with HHD followed from 1999 to 2011, found that most adverse events occur in patients with a fistula and were often the result of needle dislodgement, followed by an air embolism,[105] all of which can contribute to both hospitalizations and mortality. Patients that use PD do not face vascular access complications however, do have higher rates of abdominal related infections such as peritonitis.[102]

2.5 Predictors of Hospitalization in Patients Using Dialysis

There are factors that increase the likelihood of a patient on dialysis being hospitalized such as age, sex, race, comorbidities, obesity, and SES. Many of these risk factors are

also related. For example, those of lower SES are more likely to be racial minorities, face greater rates of obesity, as well as have greater comorbidities.

2.5.1 Age

As discussed previously, older age is a risk factor for KF. Age is also a risk factor for being hospitalized while on dialysis.[106] Older adults often have higher comorbidity burden, which is also a risk factor for hospitalization. It has been shown that elderly patients (>75 years) experience a high rate of hospitalization.[24] A historical study completed by Rocco et al. found that the risk of being hospitalized while receiving dialysis increased with age.[87]

2.5.2 Sex

Females in the general population often live longer than males. Hecking et al. suggests that this survival advantage is attenuated in those with KF.[38] Females receiving HD in the US have a 20% higher all-cause hospitalization rate than males, as well as a higher rate of infection related hospitalization regardless of modality.[37] In a national Canadian retrospective cohort study by Molnar et al., females receiving dialysis had a higher risk of all-cause hospitalization than males (HR: 1.08, 95% CI 1.05-1.11).[24] A large cohort study of patients using incident HD in the US from 2007 to 2011 found that 73% of the cohort was hospitalized at least once during follow up and the unadjusted rate of hospitalization was 1.68 PPY for males (95% CI 1.67-1.68) and 2.08 PPY for females (95% CI 2.07-2.09), with younger females having especially high hospitalization rates.[107]

While the reasoning behind sex differences and hospitalization among patients using dialysis is not entirely understood, it is thought there are both biological, clinical, and social circumstances contributing to the higher hospitalization rates in females. First, females are more prone to certain autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and sickle cell anemia, all of which can affect the kidneys[108] and contribute to comorbidity and subsequent hospitalization. Serum albumin levels have been found to differ by sex, suggesting that females may be of poorer health status while on dialysis,[107] and therefore at increased risk for hospitalization. Building on

this point, males have been found to have greater comorbidity, a quicker disease progression[37,38] and are also more likely to smoke.[37,38,108] It is possible that the sickest males have died before dialysis initiation and therefore the "healthier" males are the ones being studied while the female cohorts would include both sick and healthy patients.

Females experience more infection related complications than males, and it has been found that females are more likely to use a catheter for dialysis access than males,[37,38] which is associated with higher rates of infection and subsequent hospitalization. Further, females have been found to receive less weekly dialysis time than males,[37] which could mean they do not experience the suggested clinical benefits of an intensive dialysis regime. The Dialysis Outcomes and Practice Patterns Study suggests that females may experience lower SES, which is associated with greater healthcare utilization.[38] Females in the cohort tended to be older, had a longer dialysis vintage than males and were less likely to be married, employed, and had less education, which are indicators of lower SES.

2.5.3 Race

Despite racial and ethnic minority groups having increased risks of KF, paradoxically, they have been found to have lower risks of both hospitalization and mortality in the literature.[24,67,109] A 2014 study investigating the relationship between both race and ethnicity and hospitalization outcomes in patients initiating HD in the US between 1995 and 2009 found that hospitalization varies by both race, ethnicity, and age group.[68] Younger Hispanics and Blacks had less comorbidities such as DM and CVD than White patients, however, in the older age groups (>80 years), comorbidities were higher. Hospitalization days and admissions varied by age group, with Hispanics having the lowest hospitalization rate and days in hospital, followed by Blacks and then Whites, in the middle age groups. Unadjusted hospitalization rates were 1.89, 2.01, and 2.07 PPY, and days in hospital were 13.91, 14.94, and 15.20, for Hispanic, Black, and White patients, respectively. However, in the older age group, Hispanic patients had higher rates all-cause hospitalization than White patients. Black people had higher hospitalization rates than White people in the youngest and oldest age groups. It is suggested this

relationship could be due to socioeconomic factors such as insurance, employment, and access to medical care as well as a lack of trust in the medical system; however, it was noted that the hospitalization difference between Black and White patients in these age groups were more was more attenuated in more modern era.

The reasoning behind these paradoxical findings is not entirely understood. One potential explanation is that racial minority groups are less likely to receive a kidney transplant than White patients, which would result in the "healthiest" White patients being censored, leaving behind a sicker White population compared to racial minorities.[67,110] Another potential explanation is that racial minorities do not receive the necessary care for KF and therefore they have died before they could receive dialysis treatment. Other potential mechanisms include biological differences such as better nutrition or less inflammation in minorities. Black patients using dialysis have been found to have a leaner body mass, higher muscle mass, better biochemical markers including higher albumin, and lower creatinine, as well as greater nutritional intake, potentially indicating less malnutrition,[111,112] all of which could be protective against being hospitalized.

2.5.4 Comorbidity

Patients using dialysis experience high comorbidity, which can lead to complications and hospitalization. In the national Canadian study looking at hospitalizations in patients using dialysis by Molnar et al., patients with comorbidities were significantly more likely to be hospitalized. Patients with CVD, congestive heart failure, cerebrovascular disease, peripheral vascular disease, and malignancy had 1.14, 1.13, 1.06, 1.16, and 1.21 times greater relative hazard of hospitalization, respectively.[24] A study completed by Clark et al. found that patients experiencing high frailty tended to have multiple comorbidities and had increased risk of hospitalization.[113] Another study found a 1.20 (95% CI 1.16-1.23) times greater risk for hospital admission for each point increase in the Charlson Comorbidity Index.[114] Diabetes is associated with increased risk of infection.[102] Obesity is also significant risk factor for morbidity, which can contribute to hospitalization.

2.5.5 Socioeconomic Status

People of lower SES often experience worse health outcomes compared to higher SES groups. Lower SES groups can experience poorer living conditions, work more laborious jobs, and are more likely to engage in risky health behaviours such as smoking and alcohol consumption,[115] all of which can contribute to developing health conditions that can result in being hospitalized. KF prevalence has been found to be greater in those of lower SES.[116] In Canada, those of lower SES have higher rates of hospitalization for chronic conditions that could have potentially been preventable hospitalizations. This implies that with appropriate care these hospitalizations could have likely been managed on an outpatient basis.[117,118] A US study conducted by Saunders et al. found that CKD patients residing in lower SES neighbourhoods experienced significantly greater hospitalization rates compared to those residing in higher SES neighbourhoods after adjusting for demographic characteristics and individual SES indicators.[119] Patients on dialysis that are of lower SES have also been found to have a greater mortality risk.[120]

2.5.6 Late Nephrology Referral

Dialysis initiation requires a timely referral to a nephrologist to ensure adequate time to select a modality, allow for education/training, and prepare dialysis access. A late referral is often defined as a referral to a nephrologist less than three months before dialysis initiation.[1,10] The Study to Assess Renal Replacement Therapy (STARRT) was a multi-center Canadian study that investigated pre-dialysis care in Canada and investigated how a suboptimal dialysis start was associated with health outcomes in the first six months of KRT across patients using either HD, HHD, or PD.[121] The majority (64.6%) of patients were followed by a nephrologist for greater than 12 months prior to KF, however. 15.3%, and 6.3% were followed for less than one month, or one to three months, respectively, meeting the definition for a late referral. Of those patients who did experience a suboptimal dialysis start, 44% were late referrals. It was also found that patients using HD were less likely to have an optimal start compared to those using PD. A 2013 study completed by Nadeau-Fredette et al. found that patients using HHD who had a suboptimal dialysis start, which was defined as beginning dialysis on a central venous catheter or in hospital, had a 2.96 (95% CI 1.50-5.85) times greater hazard ratio of

experiencing earlier hospitalization, technique failure, or death compared to patients with an optimal start after adjusting for age, race, sex, and comorbidities.[122]

2.6 Rationale and Knowledge Gap

As home dialysis use continues to rise in Canada and internationally, understanding comparative outcomes with these modalities is crucial. Frequent hospitalizations are expensive and negatively impact patient QOL. Understanding if HHD has lower hospitalizations than PD is useful to both patients and clinicians when deciding on treatment options, especially where both are being considered. Further, understanding why a certain home modality may contribute to greater hospitalizations can help determine where to target resources to prevent future hospitalizations for patients receiving that therapy. While PD has been in use for a while, HHD is re-emerging as a popular dialysis option. Comparative studies between PD and HHD are scarce and tend to focus on mortality. While a few studies comparing hospitalization outcomes between PD and HHD have been done,[61,71,75,85] they have had small sample sizes, were only done in a single center, or were completed in a different country. One national Canadian study looking at hospitalization outcomes has been done; however, it did not look at HHD as at the time there were insufficient patients receiving that treatment. Our study also explored sex and racial differences between home modalities, which few other studies have done. Therefore, to the best of our knowledge, this was the first national Canadian study looking at comparative hospitalization outcomes in the home dialysis population.

Looking at hospitalization outcomes across eras allowed us to see if trends have changed over time. To our knowledge, hospitalizations in patients using home dialysis have not been extensively studied across eras. Weinhandl et al. compared hospitalization in HHD versus in-center HD in two eras (2006-2007 and 2008-2009), and found no differences;[83] however, the follow up time was short, and would not be expected to show an era effect. A study comparing mortality in HHD and PD across era found the differences between the two groups attenuated in more modern times.[10] Our hypothesis was that there was potential that we may see an increase in hospitalizations in more modern eras due to an increase in older and sicker patients being placed on home modalities, most notably

HHD. However, as dialysis technology has improved, any hospitalization differences in HHD and PD may be attenuated in more modern eras compared to more historical times.

Chapter 3: Methods

3.1 Objectives

The present thesis had two objectives which aimed to answer the following research question: do all-cause hospitalizations (hospitalization rates, days in hospital, and time to first hospitalization) differ between incident home dialysis modalities (PD or HHD) and have these patterns changed over time?

3.1.1 Objective One

To compare all-cause hospitalization (hospitalization rates, days in hospital, and time to first hospitalization) between patients using incident PD or HHD.

3.1.2 Objective Two

To compare if all-cause hospitalization (hospitalization rates, days in hospital, and time to first hospitalization) in patients using incident PD or HHD was modified by sex, race, and era of dialysis initiation, respectively.

3.2 Design and Population

We conducted a retrospective national cohort study of all adult patients with KF who initiated home dialysis within 90 days of KRT start, between January 1, 2005, to December 31, 2018, in Canada (excluding Quebec and Manitoba). Data on outcomes of interest were captured until July 1, 2020. Data were obtained from the administrative databases including the Canadian Organ Replacement Register (CORR) and the Discharge Abstract Database (DAD). Both databases are managed by the Canadian Institute for Health Information (CIHI). The data in the CORR and the DAD were previously linked by health card numbers by CIHI prior to analysis. The CORR is a longitudinal national administrative database of both center and patient level data for all individuals living with end-stage organ failure in Canada,[123] with the exception of Quebec and Manitoba due to a lack of inclusion in the CORR database for the years covering the cohort for Quebec, and the inability to link hospitalization data for Manitoba. The CORR has been previously validated for clinical research.[124] CORR

patients are followed from initial treatment until death. The CORR retrospectively collects information on demographics, clinical and outcome related data as well as transplantation, donation, and KRT data. To collect data pertaining to patients with KF receiving KRT, an initial registration form is completed and a follow up form is completed annually by care providers.[51] A change of status form is completed when a patient dies, receives a transplant, or changes dialysis modality.

The DAD contains administrative, clinical, and demographic information on hospital discharges and the most responsible diagnosis (using ICD-10 CA codes) for all patients in Canada.[125] Information for the DAD was received directly from acute care facilities from their health authorities. For the years of inclusion, all provinces and territories were required to report, except for Quebec. All dates in the CORR and DAD were randomly shifted by 15 days as part of the data de-identification process; however, the time interval between dates (e.g., the date between dialysis start and a hospital admission) remained the same.

3.3 Exclusion Criteria (Primary Analyses)

Those who had no exposure to either PD or HHD after 90 days of initiating KRT were excluded, as well as those who had previously received a kidney transplant.[102] Patients who belonged to the age group 15-19 (median age of 17 years) or less at dialysis initiation, and those who had sex coded as “other” were also excluded. Appendix 2 contains a flowchart of the exclusion process.

3.4 Ethics

Ethics approval for use of the linked dataset was previously granted to co-supervisor Dr. Karthik Tennankore through the Nova Scotia Health Authority Ethics Board (NSHA-REB) (REB file # 1025033). My name was added as a research team member on November 5, 2021.

3.5 Exposure Variable

The exposure variable of interest was incident home dialysis modality (PD or HHD), which means those patients initiating home dialysis for the first time. Many patients using home dialysis, especially HHD, do not immediately initiate dialysis at home, rather they receive in-center dialysis for a brief time before transitioning to home. Therefore, to avoid excluding patients who may have started in-center HD but were intending to initiate with home dialysis, the exposure was defined as all patients who were on home dialysis by day 90 after initiation of KRT as commonly defined in similar studies in this field.[10,71]

The exposure variable was derived from the response options on the CORR initial registration form for chronic renal failure patients on renal replacement therapy (appendix 3). Clinicians must indicate the location the patient received dialysis with the options of acute care hospital, chronic care hospital, community centre, and at home. Clinicians must also select a response to the type of category with the options of conventional HD, short-daily HD, slow-nocturnal HD, CAPD, APD, and PD combined with HD. A change in status form was submitted when a patient switched modalities, which captured the required data for patients who switched from in-center to home dialysis within 90 days. For this study, HHD was defined as any hemodialysis completed at home. All HHD types were combined into one variable for multiple reasons. The first reason was the anticipation of a small sample size of HHD subgroups and therefore combing them resulted in greater statistical power. The second was to account for the lack of standardized HHD category definitions and for the reasoning that HHD prescriptions frequently change and patients may be prescribed a treatment but are not following it.[55] Lastly, it was not anticipated that hospitalization outcomes would vary based on subtype as evidenced in a previous study and therefore stratification by subtype was not required.[91] Peritoneal dialysis included both CAPD and APD, as these modalities are commonly combined in the literature.[91] Table 1 provides a detailed description of how the exposure was defined and coded.

3.6 Outcome Variables

The outcome variables of interest were all-cause hospitalization rate, cumulative days in hospital, and the time to the first hospitalization. Hospitalization rates and days in hospital included all hospitalizations that occurred in patients while receiving home dialysis during the follow-up period. For patients that had multiple hospitalizations, time to the first hospitalization only included the initial hospitalization. Table 2 provides a detailed description of how the outcomes were defined and coded.

3.7 Covariable Assessment

Covariables included in the adjusted multivariable models were selected a priori based on a review of the literature[10,11,24,81,85,91,102,113] and a Directed Acyclic Graph (DAG) (appendix 1). Selected covariables were those collected at baseline and time-varying covariables were not updated in this thesis as they were not captured in the CORR, except for dialysis access which was poorly captured.[74] Covariables included age, sex, race, cause of KF, relevant comorbidities, body mass index (BMI), era of dialysis initiation, late referral to a nephrologist, and income quintile. A list of the covariables and how they were coded for analysis can be found in table 3. For privacy reasons, age in the CORR was a continuous variable coded as the median value of five-year age groups. Both race and sex were physician identified on the initial registration form. Race in CORR was stated as White, Black, or other; however, for this thesis was defined as a binary variable with “yes” being if the patient represented the majority racial group (non-Hispanic White in the CORR) and “no” being if the patient represented a minority racial group (Black or other). Cause of KF was categorized into the main primary reasons for KF; see appendix 3 for specific causes that fall under each category. Comorbidities in CORR were based on presence or absence of a given condition at initiation of KRT. Late nephrology referral was defined as a referral to a nephrologist less than three months prior to initiating KRT, as commonly defined in the literature.[1,10] Income quintile was a derived variable in the CORR created from the patient's postal code to estimate patient level household income based on neighbourhood income levels.[24]

3.8 Power Calculation

The exact sample size of the study population was not known prior to analysis and therefore the power calculations were based on the best estimate of what the anticipated sample size would be. In a two-sided test (alpha=0.05) with a sample size of approximately 11,676 participants (n= 11,321 PD, n= 355 HHD), an approximate standard deviation of 0.172, an R^2 of 0.1, and the probability of being hospitalized of 59% while receiving dialysis,[81] we had 98.9% power to detect a hazard ratio of 0.73 (from previous research[75]) or 20.3% power to detect a hazard ratio of 0.92 (from previous research[61]) comparing HHD to PD. Using the same sample size, standard deviation and R^2 parameters above, and assuming 80% power, we were able to detect an approximate hazard ratio of 0.81.

3.9 Statistical Analysis

All statistical analyses were conducted using Stata/SE software version 17.0 (StataCorp. 2021. *Stata Statistical Software: Release 17.0.* College Station, TX: StataCorp LLC).

Descriptive statistics were reported stratified by home modality. The follow up period for the primary analyses began at initiation of home dialysis. Patients were followed until transplant, death, withdrawal from dialysis, treatment failure, loss to follow-up or end of the study period (July 1, 2020). Patients who switched dialysis modalities (referred to as treatment failure), were censored only if the switch lasted at least 30 days or resulted in death. If a patient using home dialysis switched back to their original home modality within 30 days, it was not considered a censoring event and any outcome events were attributed the home modality the patient was using.

3.9.1 Objective One

Hospitalization rates for both PD and HHD, respectively, were calculated by dividing the total number of hospitalization events by the total time at risk and reported as a count per 1000 patient-days. Days in hospital for both PD and HHD, respectively were calculated as total number of days spent in hospital divided by the total time at risk and reported as

count per 1000 patient-days. Patients who experienced no hospitalization events only contributed to the total time at risk.

Comparison of the hospitalization rates and days in hospital between patients treated with PD or HHD was done using multivariable negative binomial regression models and reported using adjusted incidence rate ratios (IRRs) with 95% confidence intervals. This modelling approach is similar to a Poisson regression, however, is more flexible as it allows for overdispersion, which is common in hospitalization data.[126,127] Some individuals are more likely to experience recurrent events than others, which violates the assumption of homogeneity in a Poisson model. The negative binomial model allows for more variability and is able to accommodate varying likeliness of repeated hospitalizations in some subjects in the population.[127,128] For repeated event data with overdispersion, negative binomial or Andersen-Gill models are preferred and are comparable when using robust standard error estimates; however, Andersen-Gill has the advantage of more complex analyses such as modelling time-varying covariables.[129] As time-varying covariables are not being updated in this analysis, the negative binomial regression was determined to be the most appropriate model. The model was assessed for both influential and implausible outliers. Model fit was assessed by comparing observed versus predicted outcome variables.[130]

Time to first hospitalization was modelled using unadjusted cumulative incidence curves and a multivariable adjusted Fine-Gray subdistribution hazard model with 95% confidence intervals. The competing risks accounted for were death or kidney transplant.[131] Cumulative incidence curves were chosen because Kaplan-Meier curves are not appropriate in the presence of competing risks as the assumption of random censoring is violated and will result in an overestimation of the outcome. The cumulative incidence function (CIF) estimates incidence while accounting for competing risks.[132] The Fine-Gray subdistribution hazard model is an extension of the Cox proportional hazards model that allows for competing risks. Although it is acknowledged that the cause-specific hazard model may be an appropriate model for rates[133] and etiologic questions,[132] the Fine-Gray subdistribution model was selected as it is considered more appropriate in the

nephrology literature when the focus is on clinical outcomes and more appropriate for predicting the occurrence of an event over an extended period of time.[134] The proportional hazard assumption was checked using Schoenfeld residuals methods and graphically checked with a log cumulative hazard plot.

Robust standard errors were used in all models to account for any potential model misspecification, such as overdispersion, which is common in count data. Using robust standard errors, results in wider confidence intervals, which allowed us to produce more conservative estimates. [135,136] To account for confounding, multivariable adjusted regression models were used. While propensity score (PS) matching is a common approach to control for confounding in the nephrology literature,[8,59,78,82,102] there is evidence to support that in the presence of censoring, PS matching may actually introduce selection bias as while the characteristics of participants may be balanced at baseline, as censoring occurs the balance between groups is likely not maintained.[137] PS matching also has the further disadvantage of reducing sample size by excluding participants who cannot be matched.[138,139] It is further supported that PS matching is most appropriate with the outcome is rare and the sample size is small.[140] An editorial of an article by Kazmi et al. that used both traditional regression modelling for confounding and PS matching to investigate the association between late nephrology referrals and mortality in KRT patients describes that both methods produced almost identical results and that in most situations PS matching has no further advantage over traditional regression modelling.[139] Therefore, as this study had a large sample size, adequate statistical power, and given the high prevalence of patients that were hospitalized, it was justified that using traditional multivariable modelling to control for relevant covariables was appropriate for the analyses.

Covariables included in the analyses defined a priori were the same for all primary models. Covariables selected for the models were determined based on a review of the literature, and consideration of both clinical significance and biological plausibility, and further informed by a DAG (appendix 1). Missing data for comorbidities were coded as "no" under the assumption that on the CORR registration form leaving a comorbidity box

blank would indicate the absence of the condition. Missing data was minimal (approximately <5%) for the remainder of variables, and therefore were handled through a complete case analysis as this is appropriate when datasets are large.[141]

3.9.2 Objective Two

Prespecified interactions were tested between home dialysis modality and the following covariables: sex, race, and era of dialysis initiation based on previous literature.[10] Interaction plots were used to visually assess the interactions. All interactions were stratified on regardless of statistical significance to assess for effect measure modification. The eras were selected by dividing the 13 years of follow up into the following categories: era 1 (2005-2009), era 2 (2010-2014), and era 3 (2015-2018).

3.9.3 Sensitivity Analyses

Sensitivity analyses were performed to compare different home dialysis exposure definitions. We repeated all analyses with the exposure defined as those who initiated home dialysis within 180 days and 365 days of KRT, respectively. We conducted an additional sensitivity analysis of including eGFR in the models to assess if this changed our findings. It was decided a priori that if adding eGFR to the models resulted in a 10% change in effect size, we would report both models. The eGFR variable was previously calculated using the CKD-EPI formula based on sex, race, age, and creatinine levels and already available in the dataset.[50] The eGFR was only measured once at initial dialysis initiation and therefore was available at the time of home dialysis transition. It is a measure of how advanced a patient's KF was at the time of dialysis initiation. Lastly, a sensitivity analysis was performed to assess if the type of baseline HHD access the patient used at dialysis initiation had any effect on hospitalization outcomes. Analyses were stratified by HHD access type to compare those receiving HHD via catheter to PD and then those receiving HHD via AV fistula or AV graft to PD.

3.10 Tables

Table 1. Exposure variable and how it was defined and coded

Exposure Variable	Definition	Variable Coding
Home dialysis modality	Initial home dialysis treatment (PD or HHD) within 90 days of KRT start, as completed by the clinician in the CORR Initial Registration Form.	0= Peritoneal Dialysis (combining CAPD and APD) 1= Home Hemodialysis (combining conventional, short daily, and slow nocturnal hemodialysis with location listed at home)

Table 2. Outcome variables for objectives and how they were defined and coded

Outcome Variable	Definition and Coding	Notes
Hospitalization rate	Rate per 1000 patient-days A count variable of hospitalizations derived from each hospital admission experienced over the follow up period.	Calculated as the number of hospitalization events / total time at risk for both PD and HHD groups, respectively.
Days in hospital	Number of days spent in hospital per 1000 patient-days This variable was a derived variable in the DAD known as calculated length of stay, which was defined as the difference in days, between admission date and discharge date.	Calculated as the number of days spent in hospital / total time at risk for both PD and HHD groups, respectively.
Time to first hospitalization	End type variable: 1= Death 2= Transplant 3= Treatment failure 4= Loss to follow up 5= Administrative end date 6= Hospitalization	This variable indicated if the patient experienced the event of interest (hospitalization), a competing event (death or kidney transplant), or a censoring event (treatment failure, loss to follow up or

Outcome Variable	Definition and Coding	Notes
		the administrative end date). The time variable was the date the patient began home dialysis to the date the patient was hospitalized or censored.
	Time: The time from initiation of home dialysis to the date of first hospital admission reported as days.	

Table 3. Covariables included in the primary analyses and how they were coded

Covariable	Coding of Variable	Notes
Age group	Continuous variable representing the median of each age group coded as: Median age of 22= 20-24 Median age of 27= 25-29 Median age of 32= 30-34 Median age of 37= 35-39 Median age of 42= 40-44 Median age of 47= 45-49 Median age of 52= 50-54 Median age of 57= 55-59 Median age of 62= 60-64 Median age of 67= 65-69 Median age of 72= 70-74 Median age of 77= 75+	Median value of the five-year age group the patient is in at initial dialysis date. An example: if someone were between the ages 5-9, they would be coded as 7.
Sex	0= Male (ref) 1= Female	
Race	0= No, not in majority racial group 1= Yes, in majority racial group (ref)	
BMI (kg/m^2)	0 = ≤18.5 1 = 18.5-24.9 (ref) 2= 25-29.9 3= ≥30	Categorized based the on Canadian Guidelines for Body Weight Classification in Adults.[142]

Covariable	Coding of Variable	Notes
Cause of KF	0 = Diabetes 1= Glomerulonephritis/ autoimmune diseases 2= Renovascular diseases 3= Congenital/hereditary renal diseases & Polycystic kidney disease 4= Other/unknown	Based on diagnosis code on the CORR initial registration form (appendix 3).
Comorbidities *Coronary artery disease* *Congestive heart failure* *Cerebrovascular disease* *Peripheral vascular disease* *Chronic obstructive lung disease* *Prior malignancy* *Hypertension*	 0= No 1= Yes 0= No 1= Yes 0= No 1= Yes 0= No 1= Yes 0= No 1= Yes 0= No 1= Yes 0= Yes 1= No	Comorbidities present at baseline at the time of KRT initiation. Defined as the presence or absence of the condition.
Era	0= 2005-2009 1= 2010-2014 2= 2015-2018	The time period in calendar years in which the patient initiated dialysis.

Covariable	Coding of Variable	Notes
Late referral	0= No (ref) 1= Yes	The date a patient first sees a nephrologist is captured on the initial registration form in the CORR. A late referral is commonly defined in the literature as a referral to a nephrologist less than three months prior to initiating KRT.[1,10]
Income quintile	5 (high) 4 3 (ref) 2 1 (low)	Derived variable in CORR, derived from patient's postal code to estimate patient level household income based on neighbourhood income levels.[24]

Chapter 4: Results

4.1 Baseline Characteristics

At baseline, there were 355 HHD and 11,329 PD patients. Within 90 days of KRT initiation, 525 in-center HD patients transitioned to HHD and 3,558 transitioned to PD. After accounting for the exclusion criteria (see appendix 2 for detailed flowchart) and removal of missing data for the variables income (n=366), race (n=482), BMI (n=801), and late nephrology referral (n= 446), the final cohort consisted of 12,708 patients treated with PD and 715 patients treated with HHD for analysis.

Baseline characteristics of the participants are described according to home modality in table 4. In our study, patients treated with HHD were younger (median age of 52, interquartile range (IQR) 47-62 vs. median age of 62 years, IQR 52-72 for PD), with more males (67.1% HHD vs. 61.4% PD), more patients belonging to the majority racial group (75.2% for HHD vs. 66.3% for PD) and more patients belonging to a high-income quintile (22.0% for HHD vs. 15.2% for PD). Patients using HHD were more likely to be obese at baseline (BMI ≥30) (40.0% vs. 29.0% for patients using PD). The most common cause of KF was diabetes for both PD (39.3%) and HHD (29.0%). Glomerulonephritis and autoimmune diseases were another leading cause of KF for patients on HHD (22.5%). Baseline comorbidities were mainly higher in patients treated with PD with 23% having coronary artery disease (14.6% for HHD), 13.1% having congestive heart failure (10.5% for HHD), 10.2% having cerebrovascular disease (6.6% for HHD), 11.8% having peripheral vascular disease (8.4% for HHD), and 7.1% having chronic obstructive pulmonary disease (4.8% for HHD). Patients using HHD had a higher prevalence of prior malignancy at 14% (compared to 10.1% for PD). The majority of the cohort was hypertensive with 85.8% of patients using HHD, and 84.9% of patients using PD reporting this comorbidity, respectively. For those patients who initiated with HHD, 51.8% initiated with an AV fistula or graft and 48.2% initiated with a CV line.

4.2 Objective One

4.2.1 Hospitalization Rate and Days in Hospital

Overall, 10,112 patients (75.3%) experienced one or more hospitalization during the follow-up period (12,464,485 total person-days at risk). Patients receiving HHD spent a median of five cumulative days in the hospital (interquartile range (IQR): 0-14) and patients receiving PD spent a median of 10 cumulative days in the hospital (IQR:1-29). Crude rates of admission and cumulative days in hospital for each modality divided by the total time at risk, as well as the corresponding multivariable-adjusted incident rate ratios (IRRs), are reported in table 5. Of the 30,107 hospital admissions, 28,877 (95.9%) occurred in patients receiving PD, while 1230 (4.1%) occurred in patients receiving HHD. Overall, those using HHD experienced a lower crude hospitalization rate of 1.85 per 1000 patient-days compared to a rate of 2.44 per 1000 patient-days for PD (IRR= 0.77, 95% confidence interval (CI) 0.70-0.84). Patients on HHD spent 15.07 days per 1000 patient-days in the hospital compared to 26.15 days per 1000 patient-days for PD (IRR= 0.75, 95% CI 0.52-1.08).

4.2.2 Time to First Hospitalization

Patients using HHD had a longer time between the initiation of home dialysis and their first hospitalization (table 5). The median follow-up time to the first hospitalization was 535 days (1.47 years) for patients using HHD compared to 414 days (1.13 years) for patients using PD. In the presence of the competing risks of death and transplant (n= 333), compared to those using PD, patients using HHD had an adjusted subdistribution hazard ratio (SHR) of 0.84 (95% CI 0.77-0.93) for experiencing a hospitalization event.

4.2.3 Interaction with Sex

Interaction terms for sex were not statistically significant for the hospitalization rate outcome (p= 0.097), the days in hospital outcome (p= 0.342), or the time to first hospitalization outcome (p= 0.365). Crude rates of admission and cumulative days in hospital for each modality divided by the total time at risk, as well as the corresponding IRRs stratified by sex are reported in table 6. For females, the admission rate was 2.18 per 1000 patient-days for HHD compared to 2.44 per 1000 patient-days for PD (IRR=

0.88, 95% CI 0.74-1.04) and 20.47 days in hospital per 1000 patient-days for HHD compared to 26.84 days in hospital per 1000 patient-days for PD (IRR= 0.94, 95% CI 0.54-1.63). For males, the admission rate was 1.72 per 1000 patient-days for HHD compared to 2.44 per 1000 patient-days for PD (IRR= 0.72 95% CI 0.64-0.81) and 12.89 days in hospital per 1000 patient-days for HHD compared to 25.68 days in hospital per 1000 patient-days for PD (IRR= 0.67, 95% CI 0.44-1.00).

Similar findings were present in the time to first hospitalization outcome. Females using HHD had a median follow up time to the first hospitalization of 445 days (1.22 years) compared to a median follow up time of 414 days (1.13 years) for PD. In the presence of the competing risks (n=109), compared to PD, female patients using HHD had an adjusted hazard of 0.92 (95% CI 0.77-1.10) for experiencing a first hospitalization event. Males using HHD had a median follow up time to first hospitalization of 560 days (1.53 years) compared to a median follow up time of 414 days (1.13 years) for PD. In the presence of the competing risks (n=224), compared to PD, male patients using HHD had an adjusted hazard of 0.80 (95% CI 0.72-0.90) for experiencing a hospitalization event.

4.2.4 Interaction with Race

Interaction terms for race were not significant in the hospitalization rate model (p=0.135), or the time to first hospitalization model (p=0.529) but were significant in the model assessing days in hospital ($p < 0.001$). For the racial minority group, the hospital admission rate was 1.43 per 1000 patient-days for patients using HHD compared to 2.24 per 1000 patient-days for PD (IRR= 0.65, 95% CI 0.53-0.81) and 11.20 days in hospital per 1000 patient-days for HHD compared to 22.82 days in hospital per 1000 patient-days for PD (IRR= 0.42, 95% CI 0.30-0.59) (table 7). For the racial majority group, the hospital admission rate was 2.02 per 1000 patient-days for HHD compared to 2.55 per 1000 patient-days for PD (IRR= 0.80 95% CI 0.72-0.89) and 16.57 days in hospital per 1000 patient-days for HHD compared to 27.95 days in hospital per 1000 patient-days for (IRR= 0.89, 95% CI 0.58-1.38).

Findings were consistent in the time to first hospitalization model. Those in the racial minority group using HHD had a median follow up time to the first hospitalization of 634 days (1.74 years) compared to 462 days (1.27 years) for PD. In the presence of the competing risks (n=84), compared to PD, patients in the racial minority group using HHD had an adjusted hazard of 0.79 (95% CI 0.66-0.96) for experiencing a hospitalization event. Those in the racial majority group using HHD had a median follow up time to the first hospitalization 500 days (1.37 years) compared to 390 days (1.07 years) for PD. In the presence of the competing risks (n=249), compared to PD, patients belonging to the racial majority group using HHD had an adjusted hazard of 0.85 (95% CI 0.76-0.95) for experiencing a hospitalization event.

4.3 Objective Two

Interaction terms for era were not significant in the hospitalization rate model (p= 0.610), the days in hospital model (p= 0.893) or the time to first hospitalization model (p= 0.475). Hospitalization events varied across eras (table 5). In the first era, the admission rate was 1.99 per 1000 patient-days for HHD compared to 2.34 per 1000 patient-days for PD (IRR= 0.95, 95% CI 0.78-1.15) and 19.69 days per 1000 patient-days for HHD compared to 27.33 days per 1000 patient-days for PD (IRR= 0.91, 95% CI 0.63-1.32). In the second era, the admission rate was 1.72 per 1000 patient-days for HHD compared to 2.58 per 1000 patient-days for PD (IRR= 0.66, 95% CI 0.57-0.76) and 12.79 days per 1000 patient-days for HHD compared to 26.23 days per 1000 patient-days for PD (IRR= 0.58, 95% CI 0.37-0.92). In the third era, the admission rate was 1.93 per 1000 patient-days for HHD compared to 2.40 per 1000 patient-days for PD (IRR= 0.80, 95% CI 0.67-0.95) and 13.15 days per 1000 patient-days for HHD compared to 24.54 days per 1000 patient-days for PD (IRR 0.81, 95% CI 0.43-1.53).

In the first era, the median follow-up time to the first hospitalization was 541 days (1.48 years) for patients using HHD compared to 386 days (1.06 years) for patients using PD (table 5). In the presence of the competing risks (n=102), compared to patients using PD, patients using HHD had an adjusted hazard of 0.85 (95% CI 0.71-1.02) for experiencing a hospitalization event. In the second era, the median follow-up time to the first

hospitalization was 591 days (1.62 years) for patients using HHD and 429 days (1.18 years) for patients using PD. In the presence of the competing risks (n=117), compared to PD, patients using HHD had an adjusted hazard of 0.74 (95% CI 0.64-0.85) for experiencing a hospitalization event. In the third era, the median follow-up time to the first hospitalization was 437 days (1.20 years) for patients using HHD and 427 days (1.17 years) for patients using PD. In the presence of the competing risks (n=114), compared to those using PD, patients using HHD had an adjusted hazard of 1.00 (95% CI 0.85-1.19) for experiencing a hospitalization event.

4.4 Sensitivity Analyses

4.4.1 Alternate Exposure Definitions

Analyses were repeated restricting the exposure to those who initiated home dialysis within 180 days of KRT initiation and 365 days of KRT initiation, respectively. These exposure definitions resulted in consistent findings to the primary analysis exposure definition (home dialysis use by 90 days of KRT initiation) and can be found in tables 8 and 9. The sample size increased with each exposure definition. The 180-day definition had a final sample size of 14,039 patients using PD and 1,058 patients using HHD. The 365-day definition had a final sample size of 15,012 patients using PD and 1,384 patients using HHD.

4.4.2 Dialysis Access

Patients receiving HHD who initiated dialysis using a CV line had higher hospitalization rates and longer hospital stays than those who initiated dialysis with a fistula or graft (table 10). For patients using HHD with a CV line, the admission rate was 2.05 per 1000 patient-days compared to 2.44 per 1000 patient-days for PD (IRR= 0.85, 95% CI 0.74-0.97) and 19.29 days per 1000 patient-days compared to 26.13 days per 1000 patient-days for PD (IRR= 1.01, 95% CI 0.61-1.67). For patients using HHD with a fistula or graft the admission rate was 1.69 per 1000 patient-days compared to 2.44 per 1000 patient-days for PD (IRR= 0.70, 95% CI 0.61-0.79) and 12.08 days per 1000 patient-days compared to 26.13 days per 1000 patient-days for PD (IRR= 0.55, 95% CI 0.32-0.93).

4.4.3 Addition of eGFR to Adjusted Models

Adding eGFR to our adjusted models did not result in any significant change in effect size (data not shown).

4.4 Result Tables

Table 4. Baseline characteristics of the study population stratified by home modality

Characteristic[a]	Home Dialysis		*P*	Missing Data
	PD (n= 14,643)	HHD (n= 875)		
Age, median years (IQR)	62 (52-72)	52 (47-62)	<0.001	0
Sex, male	8990 (61.4)	587 (67.1)	0.001	0
Race, racial majority group	9384 (66.3)	637 (75.2)	<0.001	523 (3.4)
BMI (kg/m^2)			<0.001	936 (6.0)
≤18.5	344 (2.5)	18 (2.3)		
18.5-24.9	4858 (35.2)	225 (28.6)		
25-29.9	4592 (33.3)	229 (29.1)		
≥30	4002 (29.0)	314 (40.0)		
Cause of KF			<0.001	0
Diabetes	5756 (39.3)	254 (29.0)		
Glomerulonephritis/ autoimmune diseases	2509 (17.1)	197 (22.5)		
Renovascular diseases	2480 (16.9)	90 (10.3)		
Congenital/hereditary/ polycystic kidney disease	1192 (8.1)	145 (16.6)		
Other/unknown	2706 (18.5)	189 (21.6)		
Comorbidities				
Coronary artery disease	3214 (23.0)	124 (14.6)	<0.001	714 (4.6)
Congestive heart failure	1800 (13.1)	87 (10.4)	0.023	955 (6.2)
Cerebrovascular disease	1405 (10.2)	56 (6.6)	0.001	861 (5.6)
Peripheral vascular disease	1627 (11.8)	71 (8.4)	0.003	914 (5.9)
Chronic obstructive lung disease	969 (7.1)	40 (4.8)	0.012	959 (6.2)
Prior malignancy	1377 (10.1)	115 (14.0)	<0.001	1108 (7.1)
Hypertension	11818 (84.9)	729 (85.8)	0.511	754 (4.9)
Era			<0.001	0
2005-2009	4514 (30.8)	166 (19.0)		
2010-2014	4902 (33.5)	396 (45.3)		
2015-2018	5227 (35.7)	313 (35.8)		
Late nephrology referral (<3 months)	1476 (10.5)	105 (12.6)	0.049	594 (3.8)
Income quintile			<0.001	366 (2.4)
5 (high)	2177 (15.2)	187 (22.0)		
4	2448 (17.1)	185 (21.8)		
3	2901 (20.3)	150 (17.7)		
2	3281 (22.9)	179 (21.1)		

Characteristic[a]	Home Dialysis		*P*	Missing Data
	PD (n= 14,643)	HHD (n= 875)		
1 (low)	3495 (24.4)	149 (17.5)		
eGFR (ml/min), median (IQR)[b]	8.2 (6.3-10.6)	7.5 (5.8-10.1)	<0.001	489 (3.2)
Dialysis access			<0.001	140 (0.9)
Central venous line		410 (48.2)		
Arteriovenous fistula or graft		441 (51.8)		
PD catheter	14527 (100)			

[a]Results are presented as count (percentage) unless specified.
[b]eGFR at kidney replacement therapy initiation.
Abbreviations: IQR, Interquartile range; BMI, body mass index; KF, kidney failure; eGFR, estimated glomerular filtration rate.

Table 5. Rate of admission, days in hospital, and time to hospitalization comparing PD to HHD in the entire cohort and across eras

	Entire Cohort (n=13,423)		Era 2005-2009 (n=3,772)		Era 2010-2014 (n=4,660)		Era 2015-2018 (n=4,991)	
	Crude Rate*	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**
Admission[a,b]								
PD	2.44	1.00 (ref)	2.34	1.00 (ref)	2.58	1.00 (ref)	2.40	1.00 (ref)
HHD	1.85	0.77 (0.70-0.84)	1.99	0.95 (0.78-1.15)	1.72	0.66 (0.57-0.76)	1.93	0.80 (0.67-0.95)
Days in hospital[a,c]								
PD	26.15	1.00 (ref)	27.23	1.00 (ref)	26.23	1.00 (ref)	24.54	1.00 (ref)
HHD	15.07	0.75 (0.52-1.08)	19.69	0.91 (0.63-1.32)	12.79	0.58 (0.37-0.92)	13.15	0.81 (0.43-1.53)
	SHR (95% CI)		**SHR (95% CI)**		**SHR (95% CI)**		**SHR (95% CI)**	
Time to first hospitalization[a,d]								
PD	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
HHD	0.84 (0.77-0.93)		0.85 (0.71-1.02)		0.74 (0.64-0.85)		1.00 (0.85-1.19)	

*Expressed as the rate per 1000 patient-days

[a]Adjusted for sex, age, race, body mass index, kidney failure cause, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, prior malignancy, hypertension, era of dialysis initiation, late nephrology referral, and income quintile.

Abbreviations: PD, peritoneal dialysis; HHD, home hemodialysis; IRR, incident rate ratio; SHR, subdistribution hazard ratio.

[b]p value for era interaction= 0.610

[c]p value for era interaction= 0.893

[d]p value for era interaction= 0.475

Table 6. Rate of admission, days in hospital, and time to hospitalization comparing PD to HHD stratified by sex

	Female (n=5,114)		Male (n=8,309)	
	Crude Rate*	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**
Admission[a,b]				
PD	2.44	1.00 (ref)	2.44	1.00 (ref)
HHD	2.18	0.88 (0.74-1.04)	1.72	0.72 (0.64-0.81)
Days in hospital[a,c]				
PD	26.84	1.00 (ref)	25.68	1.00 (ref)
HHD	20.47	0.94 (0.54-1.63)	12.89	0.67 (0.44-1.00)
	SHR (95% CI)		**SHR (95% CI)**	
Time to first hospitalization[a,d]				
PD	1.00 (ref)		1.00 (ref)	
HHD	0.92 (0.77-1.10)		0.80 (0.72-0.90)	

*Expressed as the rate per 1000 patient-days

[a]Adjusted for age, race, body mass index, kidney failure cause, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, prior malignancy, hypertension, era of dialysis initiation, late nephrology referral, and income quintile.

Abbreviations: PD, peritoneal dialysis; HHD, home hemodialysis; IRR, incident rate ratio; SHR, subdistribution hazard ratio.

[b]p value for sex interaction= 0.097

[c]p value for sex interaction= 0.342

[d]p value for sex interaction= 0.365

Table 7. Rate of admission, days in hospital, and time to hospitalization comparing PD to HHD stratified by race

	Racial Minority (n=4,463)		Racial Majority (n=8,960)	
	Crude Rate*	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**
Admission[a,b]				
PD	2.24	1.00 (ref)	2.55	1.00 (ref)
HHD	1.43	0.65 (0.53-0.81)	2.02	0.80 (0.72-0.89)
Days in hospital[a,c]				
PD	22.82	1.00 (ref)	27.95	1.00 (ref)
HHD	11.20	0.42 (0.30-0.59)	16.57	0.89 (0.58-1.38)
	SHR (95% CI)		**SHR (95% CI)**	
Time to first hospitalization[a,d]				
PD	1.00 (ref)		1.00 (ref)	
HHD	0.79 (0.66-0.96)		0.85 (0.76-0.95)	

*Expressed as the rate per 1000 patient-days

[a]Adjusted for sex, age, body mass index, kidney failure cause, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, prior malignancy, hypertension, era of dialysis initiation, late nephrology referral, and income quintile.

Abbreviations: PD, peritoneal dialysis; HHD, home hemodialysis; IRR, incident rate ratio; SHR, subdistribution hazard ratio.

[b]p value for race interaction= 0.135

[c]p value for race interaction= <0.001

[d]p value for race interaction= 0.529

Table 8. Rate of admission, days in hospital, and time to hospitalization comparing PD to HHD using 180-day exposure definition

	Entire Cohort (n=15,097)		Era 2005-2009 (n=4,195)		Era 2010-2014 (n=5,287)		Era 2015-2018 (n=5,615)	
	Crude Rate*	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**
Admission[a,b]								
PD	2.48	1.00 (ref)	2.39	1.00 (ref)	2.61	1.00 (ref)	2.41	1.00 (ref)
HHD	1.89	0.77 (0.70-0.84)	1.94	0.85 (0.72-1.01)	1.78	0.68 (0.60-0.78)	2.00	0.81 (0.70-0.95)
Days in hospital[a,c]								
PD	26.58	1.00 (ref)	27.86	1.00 (ref)	26.64	1.00 (ref)	24.74	1.00 (ref)
HHD	15.26	0.68 (0.51-0.90)	18.15	0.71 (0.51-0.98)	13.47	0.56 (0.38-0.82)	14.55	0.80 (0.51-1.23)
	SHR (95% CI)		**SHR (95% CI)**		**SHR (95% CI)**		**SHR (95% CI)**	
Time to first hospitalization[a,d]								
PD	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
HHD	0.84 (0.77-0.91)		0.81 (0.69-0.95)		0.76 (0.67-0.87)		0.97 (0.84-1.12)	

*Expressed as the rate per 1000 patient-days

[a]Adjusted for sex, age, race, body mass index, kidney failure cause, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, prior malignancy, hypertension, era of dialysis initiation, late nephrology referral, and income quintile.

Abbreviations: PD, peritoneal dialysis; HHD, home hemodialysis; IRR, incident rate ratio; SHR, subdistribution hazard ratio.

[b]p value for era interaction= 0.658

[c]p value for era interaction= 0.447

[d]p value for era interaction= 0.981

Table 9. Rate of admission, days in hospital, and time to hospitalization comparing PD to HHD using 365-day exposure definition

	Entire Cohort (n=16,396)		Era 2005-2009 (n=4,549)		Era 2010-2014 (n=5,763)		Era 2015-2018 (n=6,084)	
	Crude Rate*	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**
Admission[a,b]								
PD	2.49	1.00 (ref)	2.41	1.00 (ref)	2.62	1.00 (ref)	2.43	1.00 (ref)
HHD	1.95	0.79 (0.73-0.86)	2.04	0.89 (0.77-1.04)	1.86	0.72 (0.64-0.82)	1.98	0.80 (0.69-0.93)
Days in hospital[a,c]								
PD	26.80	1.00 (ref)	28.19	1.00 (ref)	26.75	1.00 (ref)	24.92	1.00 (ref)
HHD	15.45	0.68 (0.53-0.87)	17.84	0.66 (0.50-0.89)	14.14	0.61 (0.44-0.85)	14.46	0.77 (0.52-1.15)
	SHR (95% CI)		**SHR (95% CI)**		**SHR (95% CI)**		**SHR (95% CI)**	
Time to first hospitalization[a,d]								
PD	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
HHD	0.87 (0.81-0.94)		0.85 (0.73-0.99)		0.81 (0.72-0.91)		0.97 (0.85-1.12)	

*Expressed as the rate per 1000 patient-days

[a]Adjusted for sex, age, race, body mass index, kidney failure cause, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, prior malignancy, hypertension, era of dialysis initiation, late nephrology referral, and income quintile.

Abbreviations: PD, peritoneal dialysis; HHD, home hemodialysis; IRR, incident rate ratio; SHR, subdistribution hazard ratio.

[b]p value for era interaction= 0.853

[c]p value for era interaction= 0.895

[d]p value for era interaction= 0.992

Table 10. Rate of admission, days in hospital between those initiated HHD with a graft or fistula compared to those who initiated HHD with a CV line

	AV Graft or Fistula		CV Line	
	Crude Rate*	**IRR (95% CI)**	**Crude Rate**	**IRR (95% CI)**
Admission[a]				
PD	2.44	1.00 (ref)	2.44	1.00 (ref)
HHD	1.69	0.70 (0.61-0.79)	2.05	0.85 (0.74-0.97)
Days in hospital[a]				
PD	26.13	1.00 (ref)	26.13	1.00 (ref)
HHD	12.08	0.55 (0.32-0.93)	19.29	1.01 (0.61-1.67)

*Expressed as the rate per 1000 patient-days

[a]Adjusted for sex, age, race, body mass index, kidney failure cause, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, prior malignancy, hypertension, era of dialysis initiation, late nephrology referral, and income quintile.

Abbreviations: HHD, home hemodialysis; PD, peritoneal dialysis; AV, arteriovenous; CV, central venous; IRR, incident rate ratio.

Chapter 5: Discussion

5.1 Overview of Primary Results

In this national Canadian retrospective cohort study, we found that patients receiving HHD had decreased hospitalization rates and a longer time to the first hospitalization compared to patients receiving PD. This finding is consistent with our hypothesis and previous literature comparing hospitalization outcomes between patients treated with PD or HHD.[61,71,75,85]

Our results are comparable to a Swedish registry study which found that patients treated with HHD had an annual admission rate of 1.7 compared to 2.8 for PD and 12.1 days in hospital per year compared to 20.3 days in hospital per year for PD.[71] The similarity of our results could be contributed to both studies using a national registry with large sample sizes that almost completely captured the entire dialysis population of interest. Patients in the Swedish registry study had a shorter median time to first hospitalization than our study, although competing risks were not accounted for in their study, which could have introduced bias into the results.

Cumulative days in hospital was not statistically significant between HHD and PD for the entire cohort in our study using the primary definition (90 days). It is possible that this is due to wider confidence intervals as a result of the use of robust standard errors. The days in hospital models were significantly different between those using HHD and PD in both the 180-day and 365-day definitions, potentially due to increased statistical power due to larger sample sizes. In our study, patients using PD spent double the median number of days in hospital compared to HHD, which could contribute to greater healthcare costs for patients treated with PD. Shorter hospital stays found in patients treated with HHD may have the potential to reduce healthcare costs related to patient admissions.

A US study by Kumar et al. found no statistically significant difference in risk of hospital admission ($p= 0.9$) or length of stay ($p= 0.8$) between patients using HHD or PD.[85] When looking at the crude rates, patients using HHD experienced 0.68 admissions PPY and 3.3

days PPY compared to 0.76 admissions PPY and 5.6 days PPY in the PD group. This study was limited by a small sample size (n= 86), which likely contributed to the statistical insignificance of the findings. Further, this study only looked at patients at one dialysis centre and only included patients using a specific type of HHD machine, which may have limited the generalizability of the findings. In another American study, patients using HHD had a 0.73 times lower hazard of hospital admission (95% CI 0.67-0.79) compared to patients using PD.[75] One additional US study found that patients using HHD had a 0.92 times lower hazard of hospital admission (95% CI 0.89-0.95) compared to patients using PD.[61] Our findings fall in between these two studies with patients treated with HHD having a 0.84 times lower hazard (95% CI 0.77-0.93) of hospital admission compared to patients treated with PD, indicating consistency of our findings with the literature and further validating that HHD is associated with improved hospitalization outcomes.

Despite the similarity of our findings with prior studies, there are differences across these studies that can lead to variations in results. Firstly, the majority of previous studies discussed above that compared hospitalization outcomes used propensity score matching to account for confounding.[61,71,75] Our study used traditional multivariable-adjusted models based on the evidence that propensity score matching can introduce bias in the presence of censoring[137] and has the disadvantage of reducing sample size by excluding participants who cannot be matched. For example, in the study by Suri et al., only 81% of patients using HHD could be matched to patients using PD,[75] which therefore excluded patients using HHD that would have otherwise been included in analysis and potentially introduced bias. Therefore, it is possible that slight differences in our findings could be due differences in matched cohorts compared to our adjusted models even though the covariables used were comparable.

There is no standard HHD definition used in the literature. Differences in how HHD was defined across studies could contribute to small discrepancies in the results due to different HHD prescriptions. For example, three of the cited studies only included those who completed daily HHD,[61,75,85] an only one provided a definition (defined in the study

4-5 days/week, 1.5–4.5 h/day).[75] In our study we included anyone who performed hemodialysis in the home, and therefore there may be differences in our HHD population that has a greater mix of HHD prescriptions compared to the others that could produce slightly different results. Our study was also the first Canadian study to compare hospitalizations in the home dialysis population and there are likely differences in patient characteristics (age, education, income, healthcare access) between the Canadian population and the American and Swedish populations cited that could produce varying results.

Nonetheless, our findings of reduced hospitalization events in patients receiving HHD adds to the growing body of literature that HHD is associated with better patient outcomes compared to other modalities. The primary rationale for this is that HHD generally involves a more intensive dialysis prescription, and therefore greater waste and fluid removal,[88] which can potentially result in improved phosphate control,[8] improved cardiovascular health,[143] reduced hypertension,[87,88] reduced anemia, and improved nutritional status.[89,90] Another potential mechanism is that HHD potentially removes the two-day interdialytic break that occurs in patients receiving in-center HD, which has been found to be followed by increased rates of hospitalization.[91] Overall, our study validates existing work on the topic while also being the first to investigate these outcomes in the Canadian home dialysis population.

5.2 The Effect of Sex on the Association of Home Dialysis and Hospitalization

Our results suggest that males are less likely to be hospitalized compared to females. Although the interaction for sex did not meet statistical significance, stratification showed that males are experiencing fewer hospitalization events than females, which is clinically significant. There were more male patients using HHD than female patients using HHD in our study, which is consistent with previous studies.[71,75] An interesting finding is that there was no difference in the crude hospitalization rate between sexes using PD, and very little difference for days in hospital; however, in those using HHD, males had both significantly lower crude hospitalization rate and days in hospital compared to females. It is not well known why differences in hospitalization outcomes between sex are most

dramatic in HHD and there is little research exploring sex differences to compare our findings to. It is known that being female is associated with higher hospitalization rates than males,[68,107] but research is lacking on the "why". Females are less likely to utilize PD and HHD than males,[38] which means there could be potential barriers females are facing to home dialysis access.

It is also plausible that the reason for such differences in hospitalization outcomes between sexes in our study is due to socioeconomic factors such as education level, access to care, social supports, and appropriate housing conditions. We were unable to assess for these factors in our study due to a lack of collection of these variables. A recent study comparing sex differences in mortality for patients using dialysis found that more males were married (72% of males vs. 47% of females) and employed (53% of males vs 39% of females) while more females were widowed (26% of females vs 7% of males) and had less than high school education (26% of females vs 18% of males).[144] As a result, females may lack the necessary supports to be successful with HHD, such as a caregiver to provide both assistance and support and therefore are experiencing more hospitalization events. Females often are the ones that provide care in the event of a chronic illness in the family.[145] A study exploring caregiver burden among patients using HD found that 65.2% of patients were male, while 56.1% of caregivers were female.[146] If females are often the ones in the caregiving role, it is possible when they become the patient they may either lack a caregiver or their caregiver (if male) may be quicker to experience caregiver burnout, which may contribute to HHD complications resulting in a hospitalization. There remains a lack of research on sex differences in medical research,[37,147,148] and dialysis research is no exception. It is known that sex differences exist in both the utilization and outcomes of dialysis, but future research must focus on exploring why these differences exist and what barriers females are facing to successful dialysis treatment and eventual transplant.

5.3 The Effect of Race on the Association of Home Dialysis and Hospitalization

In our study, racial minorities experienced significantly less days spent in hospital compared to those in the racial majority group. This finding was most profound in racial

minorities using HHD. The difference was less pronounced in the time to first hospitalization analysis, although, racial minorities still had a lower hazard of admission and less competing events than those belonging to the racial majority group. Our findings are consistent with the literature where racial minority groups have been found to have less hospitalizations and improved survival compared to White patients.[67,68,109,110]

A 2014 study by Yan et al. assessing differences in hospitalizations across racial and ethnic groups receiving in-center HD found that those patients identifying as Hispanic had the lowest rates of hospital admission (adjusted risk ratio (aRR)= 0.89, 95% CI 0.88-0.90) and days in hospital (aRR= 0.91, 95% CI 0.90-0.93), followed by Black patients for both hospital admission (aRR= 0.95, 95% CI 0.94-0.96) and days in hospital (aRR= 1.01, 95% CI 0.99-1.02) compared to White patients. This is a less pronounced rate ratio than our findings; however, this study was only looking at in-center HD, was limited by a short follow up time (median of one year follow up), and stratifying by multiple racial groups may have decreased statistical power. They also found that this relationship between race and hospitalizations was modified by age. In the youngest and oldest age groups, Black patients had the greatest hospitalization outcomes. It is plausible that this paradox of better outcomes for racial minorities is modified by different characteristics across age groups such as socioeconomic factors like employment status, living conditions, and access to health care.

Racial minorities are less likely to receive a kidney transplant compared to White patients.[67] As a result, it is possible that racial minorities on dialysis also contain healthier patients compared to White patients, because the healthiest White patients have been transplanted leaving behind a sicker, White dialysis population. Transplant was accounted for as a competing risk in our time to first hospitalization model, which should have reduced this bias; however, in other models (hospitalization rate, and days in hospital) it was not and therefore could have affected our findings. Racial minorities were much less likely to experience a competing risk in our study compared to those belonging to the racial minority group.

Alternatively, it is known that CKD is more prevalent in racial minority groups and progresses to KF faster,[19] therefore another important consideration is that the sickest patients in the racial minority group may have died before they received appropriate care and initiated dialysis, resulting in a survival bias. Another potential explanation for the improved outcomes in racial minority groups is the higher rate of dialysis discontinuation in White patients compared to those belonging to other racial groups.[149] When comparing survival after hospitalization between racial groups, Agunbiade et al. found that when discontinuation of dialysis was accounted for in analyses, the survival differences between races was greatly attenuated.

Our findings may also be contributed to societal factors such as SES due to ongoing racism rather than biological mechanisms.[110] Shen et al. determined that SES factors such as measures of poverty, education, employment, and segregation contributed to why racial minorities are less likely to initiate HHD than White patients.[66] Unfortunately, our study had limited information on SES and could not assess these factors.

There are potential biological mechanisms that may have also contributed to our findings. It has been proposed that differences in nutritional and dietary factors across racial groups may contribute to differences in health outcomes.[111,112] Black patients have been found to have higher levels of pre-dialysis serum albumin, which can indicate better health status.[111] They have also been found to have higher consumption of energy and fat, which may be indicative of better nutritional status prior to dialysis initiation. However, it is also important to recognize that both race and ethnicity are social and political constructs[150] and using this terminology to assess for biological differences in health outcomes may not be appropriate or correct.[151] Additionally, as race was physician identified in this study, these results should be interpreted with caution. Future research should focus on correctly capturing and interpreting race-based data to better understand the relationship between race and health outcomes patients on dialysis.

5.4 The Effect of Era on the Association of Home Dialysis and Hospitalization

Hospitalization outcomes varied across the three eras in our study, although patients receiving PD consistently experienced greater hospitalization events than those receiving HHD. We had initially hypothesized that we would see an increase in hospitalization events in more modern eras as older patients with a higher comorbidity burden and frailty are being placed on home modalities, specifically HHD. We also suspected that hospitalization differences between HHD and PD would be decreased in modern eras due to improvements in home dialysis technology.

Contrary to our hypothesis, hospitalization outcomes did not consistently increase in a linear fashion across eras. For patients using PD, the number of crude cumulative days in hospital decreased over time, although this is not a trend that was observed in the hospitalization rate model or in patients using HHD. PD has been the primary home modality for many years and over the past several years there has been significant research to develop evidence-based clinical practice guidelines that have addressed access issues and focused on preventing and managing infection, which has resulted in improved quality of PD.[152] This could be the reason why we found improved or consistent hospitalization outcomes in patients receiving PD over time.

We found that the earliest era (2005-2009) had the highest crude rate of hospitalization and days in hospital for patients using HHD although this was not statistically significant. This era had the smallest difference in hospitalizations between PD and HHD. There are a few potential reasons for this finding. First, HHD technology was likely not as advanced at this time, with patients using HHD potentially experiencing more complications resulting in the need to be hospitalized. Many physicians may have not been as familiar with HHD training yet and patients may not have received as much education prior to HHD initiation as they would have in more modern eras, which could have resulted in more access issues requiring hospitalization. Further, at this time there was likely less emphasis on available nursing support to help maintain patients at home.

In the middle era (2010-2014), we saw the largest difference in hospitalizations between PD and HHD, with patients using HHD having substantially less admissions and days in hospital than in the first era. This is potentially reflecting that HHD was still mainly reserved for the healthiest patients at this time. Patients using PD also had a higher admission rate in this era compared to the first, which could be reflecting more patients beginning to prefer a home modality in the face of easing criteria for selection to PD. In Ontario, a home first dialysis initiative was launched in 2012 which led to a 25% increase in PD prevalence.[153]

Today, many patients using home dialysis have access to 24-hour on-call nursing support to assist with any issues and help solve problems at home.[154] There have also been advancements in HHD technology to make it more user friendly and both patients and physicians may be better at troubleshooting and managing small problems at home due to extensive HHD training prior to initiation.[155] Virtual care treatment and management options may have also contributed to less hospital admissions in the more modern eras as telemedicine and remote patient monitoring systems have become more common.[156–160] These are potential reasons contributing to why patients using HHD in the most modern era (2015-2018) had less hospitalization events than those in the earliest. Despite statistical insignificance, this is a clinically relevant finding as it shows that patients using HHD may be having better outcomes compared to previous historical eras.

The most modern era also likely saw a shift in the HHD dialysis population when older and sicker patients began utilizing this treatment more, which is likely the reasoning for the smaller difference in hospitalizations between HHD and PD at this time. Other studies have reported that patients initiating HHD in more modern times are older, with more comorbidities than those who initiated in the past.[74] Another important point of consideration is that the most modern era may have had the shortest follow up time in our study. Considering we found that patients using HHD had a longer time to their first hospitalization than PD, it is possible that if we had followed the modern era longer, we would have captured more HHD hospitalizations and potentially seen less of a difference in hospitalizations between the two modalities.

Few other studies have looked at trends across eras and those that did were often mortality focused. A recent study comparing survival between patients using either PD or HHD across eras found that mortality differences attenuated over time.[10] A study completed by Perl et al. in 2017 investigating trends in patient survival in patients using HHD in Canada found no differences in survival across eras.[74] However, the most modern era in this study was 2008-2012 and therefore it is possible that they did not capture the shift in patient characteristics that has occurred in patients initiating HHD in more modern times. One study that did look at hospitalization differences between HHD and in-center HD in the United States found no statistical difference in hospitalization rates across two eras (2006-2007, 2008-2009); however, the follow up time was short and would likely not have shown an era effect over this limited time period.[83] Additionally, using in-center HD as the comparative group may have resulted in bias due to patient demographic differences between these two groups. It appears we are the first to study hospitalization differences between home dialysis modalities across eras in depth. We believe our findings regarding hospitalizations differences across eras are likely due to the known change in characteristics (older and sicker) of patients choosing HHD in more modern times as well as the lessening of HHD criteria over time and advancements in home dialysis technology; however, future studies should confirm these findings.

5.5 Sensitivity Analyses

5.5.1 The Effect of HHD Access on Home Dialysis and Hospitalization

As expected, patients that initiated HHD with a CV line, had much higher hospitalization rates and days in hospital than those who initiated with an AV fistula or graft. There is literature supporting that PD has a survival advantage over HD in the initial one to two years after dialysis initiation.[89,161,162] Perl et al. suggested this relationship is modified based on HD vascular access.[163] In a CORR registry study published in 2011, Perl et al. identified that those who began HD with a catheter had significantly higher one-year mortality compared to PD; however, those who initiated HD with an AV fistula or graft had similar one-year mortality to PD.[163] Our findings are therefore similar to Perl et al. when applied to hospitalization outcomes. This is an important contribution to the literature as there is potential to reduce the number of hospitalizations patients experience

if they begin their dialysis with a fistula or graft rather than a CV line, which is associated with higher rates of both infection and mortality.[164]

5.5.2 Different Exposure Definition Assessment

Re-running the analyses with 180-day and 365-day exposure definitions resulted in similar results to the primary 90-day exposure definition. In the days in hospital model, the effect was significant for both the 180-day (IRR= 0.68, 95% CI 0.51-0.90) and 365-day (IRR= 0.68, 95% CI 0.53-0.87) compared to the primary 90-day definition which was not statistically significant (IRR= 0.75, 95% CI 0.52-1.08). This could be contributed to the higher risk period of hospitalization events when dialysis is newly initiated; however, this was not observed for the hospitalization rate, which was lower for the 90-day and 180-day definitions compared to the 365-day definition. It is possible that people hospitalized sooner within initiating KRT require more complex care resulting in longer hospital stays compared to those who have been on dialysis longer. When looking at the time to first hospitalization models the 365-day definition had the most competing events, which is expected because as time goes on people are more likely to be transplanted or die.

Assessing different exposure definitions is good practice as there is no consistent definition used in the literature. Restricting the analysis to a short exposure definition could result in missing patients who have not transitioned to home dialysis yet but restricting the analysis to a longer exposure definition risks survivor bias as patients must survive the high risk post-KRT initiation period to be captured. However, as shown in our study, the exposure definition did not greatly alter our findings.

5.6 Limitations and Strengths

Our study has some notable limitations. Firstly, using an administrative database means our study was observational in nature, and our analyses were limited to the data collected. The CORR does not collect information on psychosocial characteristics, and there was limited information regarding SES. As discussed previously, patients may be more inclined to choose a home dialysis option if they have a caregiver to assist them, either

emotionally or physically with their treatment.[65] It is possible that patients who have a caregiver to assist them with home dialysis have different hospitalization outcomes than those who lack caregiver support; however, we were unable account for this in our study as this was not captured in the data. We were also missing data from two key provinces (Quebec and Manitoba), which may have compromised the generalizability of our findings. The variables race and sex were provider identified, which leaves the potential for misclassification bias. Dialysis modality was only assessed at baseline, thus increasing the potential for misclassification errors; however, any modality switches lasting longer than 30 days were censored. Additionally, it is understood that this type of study has potential for survivor bias[165] because patients must have survived up to the point of home dialysis initiation to be included in the study.

Our study only assessed all-cause hospitalizations and therefore is inclusive of hospitalization events that were not attributable to the exposure. Lastly, it is beyond the scope of our study to imply a cause and effect on the relationship between home dialysis and hospitalizations. We cannot say with certainty that there is not residual confounding contributing to patients treated with HHD having lower hospitalization outcomes as it is well known this population tends to be healthier and therefore is already less likely to experience hospitalization events.

Despite these limitations, this thesis has several important strengths. It used a national database with a large sample size that had been previously linked and validated for research. To our knowledge, this is the first national Canadian study comparing hospitalization outcomes in patients using home dialysis with a prespecified era effect assessment and therefore contributes new knowledge to this field of research. The linking of the CORR and the DAD allowed us to control for many covariables. We completed several pre-specified sensitivity analyses to test the robustness of our findings. Survival bias was mitigated in our study by using an early home dialysis definition (within 90 days of KRT), which helped ensure we were capturing those in the high-risk period of adverse outcomes. Additionally, testing our results with two different exposure definitions

(initiation within 180 and 365-days, respectively), also helped ensure our resulted were not biased by survivorship.

5.7 Study Implications

Home dialysis use has increased in recent years and is likely to continue to rise as more countries promote a home-first approach. Therefore, it is important to understand differences in clinical outcomes between PD and HHD. The findings from this thesis build on existing research demonstrating that HHD is associated with improved health outcomes when compared to PD. Findings from our study may be used in patient education to help patients make an informed modality selection. Future research should assess cause-specific hospitalizations to provide a more in-depth understandings of hospitalization differences between home modalities. Additionally, future studies must take into consideration the differences between sex and racial groups and dive deeper into the reasons underpinning these differences.

5.8 Conclusion

This national Canadian cohort study of incident home dialysis patients found that patients on HHD experienced less hospital admissions, fewer days in hospital, and a longer time to first hospitalization when compared to patients using PD. These findings were most pronounced in male patients and in those belonging to a racial minority group. Although not statistically significant, patients in the most modern era had less hospitalization events than those in earliest era.

5.9 Knowledge Translation

This thesis was presented in virtual poster format during the Department of Medicine Research Week at Dalhousie University. This completed thesis will result in two publications. The first will be a manuscript with the major findings of this study, which will be prepared and submitted to relevant peer-reviewed journals. The second will be a review article of hospitalization outcomes in patients using home dialysis that will also be

submitted to relevant peer-reviewed journals. Additionally, findings will be presented at a relevant research conference.

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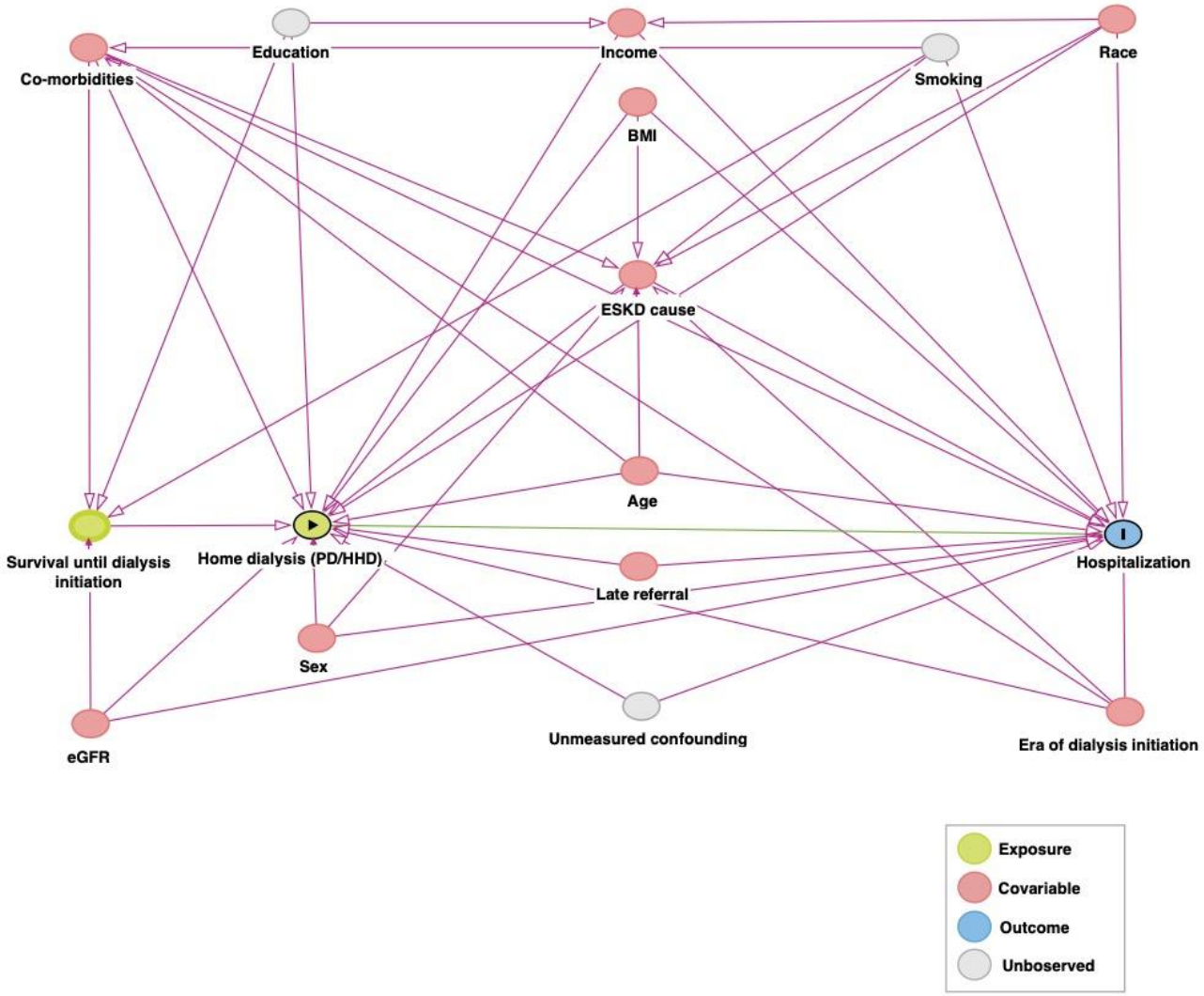
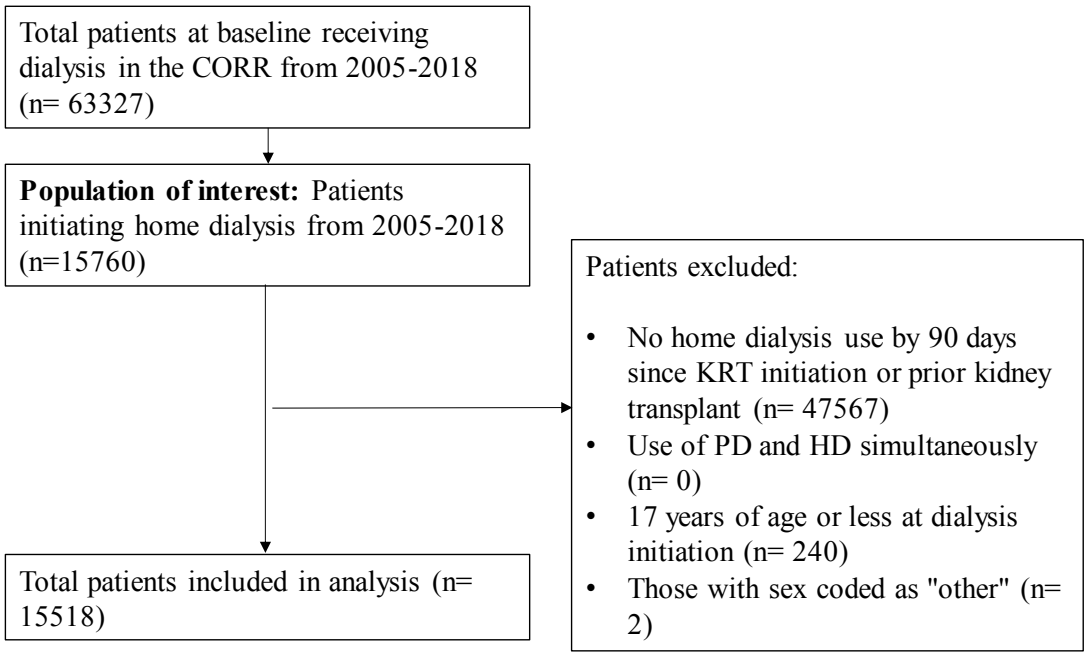
Appendix 1: Simplified DAG of Covariables and the Relationship with the Exposure and Outcome Variables



Appendix 2: Flowchart of exclusion Criteria for the Primary Analyses



Appendix 3: CORR Initial Registration Form for Chronic Renal Failure Patients on Renal Replacement Therapy

Canadian Organ Replacement Register
Chronic Renal Failure Patients on
Renal Replacement Therapy

INITIAL REGISTRATION—2020

This form is for reference only.
CORR accepts only electronic submissions.

Hospital Name: _____

SECTION A—PERSONAL IDENTIFICATION

Patient Last Name: _____

Patient Former Name: _____

Patient First and Middle Names: _____

Patient Address *(city and province only)*: _____

Patient Postal Code: |__|__|__| |__|__|__|

Health Card Number: _____

Province of Health Card: _____

Date of Birth: |__|__|/|__|__|__|/|__|__|__|__| (DD/MON/YYYY)

Sex *(check one)*: ○ Male ○ Female ○ Other

Race *(check one)*:
○ Caucasian/white (01) ○ Asian (02)
○ Black (03) ○ Indian Sub-continent (05) ○ Pacific Islander (08)
○ Aboriginal (09) ○ Mid-East/Arabian (10) ○ Latin American (11)
○ Unknown (98) ○ Other/Multiracial (99) _____

SECTION B—PRE-DIALYSIS AND INITIAL BLOOD WORK

Date when patient first seen by nephrologist:
|__|__|/|__|__|__|/|__|__|__|__| (DD/MON/YYYY)

Was patient followed by a nephrologist prior to initiating dialysis?

(check one):
○ no pre-dialysis follow-up (0)
○ yes followed in nephrologist's office (1)
○ yes followed in speciality clinic (2)
○ yes followed in both office and clinic (3)
○ unknown (9)

Was the patient receiving erythropoietin (i.e. Eprex, Aranesp) prior to initial dialysis treatment?

○ no ○ yes ○ unknown

If yes:

○ Eprex ○ Aranesp ○ Other

Last blood work before initial dialysis treatment: *(Indicate NA if not available)*

Haemoglobin (g/L) _____ Creatinine (µmol/L) _____

Urea (mmol/L) _____ Serum Bicarbonate/CO_2 (mmol/L) _____

Serum Calcium (mmol/L) _____ ○ uncorrected ○ corrected ○ ionized

Serum Phosphate (mmol/L) _____ Serum Albumin (g/L) _____

Serum Parathormone (PTH) _____ ○ pmol/L ○ ng/L ○ pg/ml

SECTION C—INITIAL AND INTENDED DIALYSIS TREATMENT

Access used at time of initial dialysis *(check one)*:

Haemodialysis
○ Temporary catheter non-cuffed (1)
○ Temporary catheter cuffed (2)
○ Permanent catheter non-cuffed (3)
○ Permanent catheter cuffed (4)
○ AV fistula (5) ○ AV graft (6)

Peritoneal Dialysis
○ PD catheter (7)

Date of first renal replacement therapy:
|__|__|/|__|__|__|/|__|__|__|__| (DD/MON/YYYY)

Initial dialysis treatment type *(Specify location, type and level of assistance/care.)*

LOCATION:
○ Acute care hospital ○ Chronic care hospital ○ Community centre ○ Home

TYPE:
○ Conventional haemo ○ Short daily haemo ○ Slow nocturnal haemo
○ CAPD ○ APD ○ Peritoneal dialysis combined with haemo

ASSISTANCE/CARE:
○ Total care ○ Limited self care ○ Total self care

Is this initial treatment the intended long-term dialysis treatment for this patient?

○ Unknown
○ Yes
○ No 〈 If not, why not?
- ○ no facilities/space available (1)
- ○ no mature access (2)
- ○ unforeseen change in patient status leading to sudden dialysis start (3)
- ○ other (specify) _____ (4)

If not, what is the long-term intended treatment for this patient? *(Specify location, type and level of assistance/care.)*

LOCATION:
○ Acute care hospital ○ Chronic care hospital ○ Community centre ○ Home

TYPE:
○ Conventional haemo ○ Short daily haemo ○ Slow nocturnal haemo
○ CAPD ○ APD ○ Peritoneal dialysis combined with haemo

ASSISTANCE/CARE
○ Total care ○ Limited self care ○ Total self care

Canadian Institute for Health Information
Institut canadien d'information sur la santé

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Form IRD2020

Patient Last Name: _____

SECTION D—HEIGHT AND WEIGHT

Height/weight cannot be provided because patient is:

○ A double-leg amputee

Record patient's height (cm) at the start of the first dialysis treatment this year:

|__|__|__|•|__|__|__| cm

Record patient's actual weight (kg) within the first month of treatment:

|__|__|__|•|__|__|__| kg

Conversion factors: 1 inch = 2.54 cm; 1 lb = 0.454 kg

SECTION E—PRIMARY DIAGNOSIS AND RISK FACTOR HISTORY

Primary renal disease *(see codes on page 3)*: |__|__|

Specify: _____

Risk Factors/Co-morbid Conditions *(check one response per condition)*:

	No	Yes	Unknown
a) Angina	○	○	○
b) Myocardial infarct	○	○	○
c) Coronary artery bypass grafts/angioplasty	○	○	○
d) Recent history of pulmonary edema *(i.e. episode(s) of congestive heart failure or pulmonary edema within 6 months prior to dialysis)*	○	○	○
e) Cerebrovascular disease *(i.e. stroke, transient ischemic attack, carotid surgery)*	○	○	○
f) Peripheral vascular disease *(i.e. previous surgery such as femoropopliteal bypass graft, iliac or femoral endarterectomy, angioplasty, etc.; ischemic muscle pain precipitated by exercise; ischemic ulcers; gangrene; amputation)*	○	○	○
g) Diabetes Type 1	○	○	○
h) Diabetes Type 2	○	○	○
i) Malignancy existing prior to first treatment	○	○	○

If yes, indicate site using the codes listed on page 3 or specify:

|__|__| _____

j) Chronic obstructive lung disease *(i.e. emphysema or chronic bronchitis)*	○	○	○
k) Receiving medication for hypertension	○	○	○
l) Other serious illness that could shorten life expectancy to less than 5 years	○	○	○

If yes, specify condition: _____

_____

m) Current smoker *(i.e. has smoked cigarettes, cigars or a pipe in the last three months)*	○	○	○

Treatment Codes

Consists of treatment location, treatment type and level of assistance/care required.

LOCATION

1 = Acute Care Hospital: Treatments carried out in a dialysis facility located in or on the grounds of a hospital that provides full renal care services (i.e. services provided under the care of nephrologist(s), which include social work and dietary consultation and inpatient back-up care).

2 = Chronic Care Hospital: Treatments carried out in a facility where ongoing medical intervention is provided and residents require assistance. Includes chronic care facilities and nursing homes.

3 = Community Centre: Dialysis done outside a hospital. Treatment may occur in an office building, shopping plaza or other place where nephrology inpatient services are not onsite. This includes mobile dialysis services, and dialysis provided at independent health facilities.

4 = Home: Treatments carried out in the patient's home by the patient and/or family member(s).

TYPE

1 = Conventional Haemodialysis: Given 3–6 hours two to four times a week.

2 = Short Daily Haemodialysis: Given during the day or evening for 2–3 hours 5 to 7 days per week.

3 = Slow Nocturnal Haemodialysis: Given 5–6 nights per week.

4 = CAPD (Continuous Ambulatory Peritoneal Dialysis): Patient receives peritoneal dialysis treatments through an implanted peritoneal catheter continuously throughout the day and night.
The fluid held in the abdominal cavity is exchanged an average of 4 times per 24 hours, with a usual volume of 2 litres (includes enhanced CAPD).

5 = APD (Automated Peritoneal Dialysis): An automated cycler is used to effect the dialysate exchanges while the patient sleeps at night with or without additional exchanges during the day. Excludes night manual exchanges and non-automated night exchanges.

6 = Peritoneal Dialysis Combined with Haemodialysis: Patient is receiving a combination of any type of peritoneal dialysis and haemodialysis.

For Type of Treatment code 6 only, location and level of assistance are to be coded as 0 (i.e. 0-6-0).

ASSISTANCE/CARE REQUIRED

1 = Total Care: Patient is under the full care of trained staff affiliated with a nephrology unit.

2 = Limited Self Care: Patient receives a minimal amount of assistance from trained staff affiliated with a nephrology unit.
This does not include family member(s).

3 = Total Self Care: Patient is completely responsible for his/her own treatment, with no assistance from nephrology trained staff.
A patient may be classified as total self care if he/she receives assistance from family member(s) or home care worker who is not a trained staff affiliated with a nephrology unit.

Examples:

An elderly, infirmed patient waiting for a chronic care bed but being treated at an acute care hospital with conventional haemodialyis would be coded: |1|1|1|.

A patient on short daily haemodialysis who is being treated at the acute care hospital with only some care provided by trained staff would be coded: |1|2|2|.

A patient on home CAPD receiving no assistance from trained staff would be coded: |4|4|3|.

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Site of Primary Malignancy Codes

11 Two or more primary malignancies

SKIN (excludes lips and genitals)

20 Squamous cell carcinoma
21 Basal cell carcinoma
22 Squamous and basal cell carcinoma
23 Malignant melanoma

LEUKAEMIAS AND RETICULOSES

25 Myeloma
26 Acute leukaemia
27 Chronic leukaemia
29 Reticulum cell sarcoma
30 Kaposi sarcoma
31 Lymphosarcoma
33 Plasma cell lymphoma
34 Hodgkin's disease
35 Lymphoreticular tumours
36 Histiocytic reticulosis

GASTRO-INTESTINAL TRACT

40 Lip
41 Tongue
42 Parotid
43 Oesophagus
44 Stomach
45 Colon
46 Rectum
47 Anus
48 Liver—primary hepatoma
49 Liver—primary lymphoma
50 Gallbladder and bile duct
51 Pancreas

NECK AND THROAT

53 Larynx
54 Thyroid
55 Bronchus
56 Lung, primary tumour

UROGENITAL TRACT

60 Kidney—Wilms' tumour
61 Kidney—Hypernephroma of host kidney
62 Kidney—Hypernephroma of graft kidney
63 Renal pelvis
64 Ureter
65 Urinary bladder
66 Urethra
67 Prostate
68 Testis
69 Penis
70 Scrotum
71 Perineum
72 Vulva
73 Vagina
74 Uterus—cervix
75 Uterus—body
76 Ovary

MISCELLANEOUS

80 Breast
81 Muscle
82 Bone
83 Brain—primary lymphoma
84 Brain—other primary tumour
85 Other tumour of central nervous system
90 Metastatic carcinoma, primary site unknown
99 Other primary tumour, specify _____

Primary Renal Diagnosis Codes

00 Chronic renal failure—aetiology uncertain

GLOMERULONEPHRITIS/ AUTOIMMUNE DISEASES

05 Mesangial proliferative glomerulonephritis
06 Minimal lesion glomerulonephritis
07 Post-strep glomerulonephritis
08 Rapidly progressive glomerulonephritis
09 Focal glomerulonephritis (adults)
10 Glomerulonephritis, histologically NOT examined
11 Severe nephrotic syndrome with focal sclerosis (paediatric patients)
12 IgA nephropathy—proven by immunofluorescence (not code 85)
13 Dense deposit disease—proven by immunofluorescence and/or electron microscopy (MPGN Type II)
14 Membranous nephropathy
15 Membranoproliferative mesangiocapillary glomerulonephritis (MPGN Type I)
16 Idiopathic crescentic glomerulonephritis (diffuse proliferative)
17 Congenital nephrosis or congenital nephrotic syndrome
19 Glomerulonephritis, histologically examined
73 Polyarteritis
74 Wegener's granulomatosis
84 Lupus erythematosus
85 Henoch-Schonlein purpura
86 Goodpasture's syndrome
87 Scleroderma
88 Haemolytic uraemic syndrome

NEPHROPATHY, DRUG-INDUCED

30 Nephropathy caused by drugs or nephrotoxic agents—cause not specified
31 Nephropathy due to analgesic drugs
32 Nephropathy due to cisplatin
33 Nephropathy due to Cyclosporin A
39 Nephropathy caused by other specific drugs

POLYCYSTIC KIDNEY

41 Polycystic kidneys, adult type (dominant)
42 Polycystic kidneys, infantile and juvenile types (recessive)

DIABETES

80 Diabetic nephropathy associated with Type 1
81 Diabetic nephropathy associated with Type 2

CONGENITAL/HEREDITARY RENAL DISEASES

21 Pyelonephritis/Interstitial nephritis associated with neurogenic bladder
22 Pyelonephritis/Interstitial nephritis due to congenital obstructive uropathy with or without vesico-ureteric reflux
24 Pyelonephritis/Interstitial nephritis due to vesico-ureteric reflux without obstruction
40 Cystic kidney disease, type unspecified
41 Polycystic kidneys, adult type (dominant)
42 Polycystic kidneys, infantile and juvenile types (recessive)
43 Medullary cystic disease, including nephronophthisis
49 Cystic kidney disease, other type
50 Hereditary/familial nephropathy, type unspecified
51 Hereditary nephritis with nerve deafness (Alport's Syndrome)
52 Cystinosis
53 Oxalosis
54 Fabry's disease
55 DRASH syndrome
58 Posterior urethral valves
59 Hereditary nephropathy
60 Congenital renal hypoplasia
61 Oligomegonephronic hypoplasia
62 Segmental renal hypoplasia (Ask-Upmark kidney)
63 Congenital renal dysplasia with or without urinary tract malformation
66 Syndrome of agenesis of abdominal muscles (Prune belly syndrome)

RENAL VASCULAR DISEASE

70 Renal vascular disease, type unspecified
71 Malignant hypertension (no primary renal disease)
72 Renal vascular disease due to hypertension (no primary renal disease)
73 Polyarteritis nodosa
78 Atheroembolic renal disease
79 Renal vascular disease, classified (nephrosclerosis, renal vascular thrombosis)

OTHER

20 Pyelonephritis/Interstitial nephritis, cause not specified
23 Pyelonephritis/Interstitial nephritis, due to acquired obstructive uropathy
25 Pyelonephritis/Interstitial nephritis, due to urolithiasis
29 Pyelonephritis, other causes
56 Sickle cell nephropathy
57 Wilms' tumour
82 Multiple myeloma
83 Amyloid
89 Multi-system disease
90 Cortical or acute tubular necrosis
91 Tuberculosis
92 Gout
93 Nephrocalcinosis and hypercalcaemic nephropathy
94 Balkan nephropathy
95 Kidney tumour
96 Traumatic or surgical loss of kidney
97 HIV nephropathy
99 Other identified renal disorder—specify _____

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