Chronic Kidney Disease Prevalence and Nephrology Service Delivery in Newfoundland and Labrador Health Regions

by

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ABSTRACT

Chronic kidney disease (CKD) is a major cause of morbidity and mortality among kidney patients in Newfoundland and Labrador (NL). This study aims to investigate the burden of CKD across geographic areas in NL and the utilization pattern for nephrology services. The ultimate goal is to inform future service planning in NL.

This is a retrospective cohort study of 40,465 CKD patients' administrative data recorded over a 5-year period (2011-15). We compared the differences in nephrology service accessibility and frequency of nephrologist visit follow-up among the four health regions. P<0.05 was considered statistically significant.

This study found that only 7.3% of NL CKD patients were in contact with nephrologists within one year of CKD being identifiable based on estimated glomerular filtration rate (eGFR). Male CKD patients have a 1.4-fold (OR, 1.4; 95% CI, 1.3-1.5 (p < 0.05) higher chance of seeing a nephrologist than female CKD patients. Among diabetic patients, only 12.8% of patients were tested for their urine albumin-creatinine ratio. On the other hand, only 4.5% of all CKD patients had a urine analysis performed. This is an underutilization of urine testing, which is a key diagnostic test that care-providers are failing to offer. Except for in the Eastern Regional Integrated Health Authority (ERIHA), patients from all other health regions faced difficulties in accessing nephrology care in their own regions.

Development of telehealth and e-health programs and decentralizing CKD early detection and risk identification and care by a robust kidney outreach program would be useful for optimal CKD care in NL.

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DEDICATION

This thesis is dedicated to my wife Farzana Fahima and my daughter Waffa Zahralyn, whose inspiration, patience and unrelenting support make me feel their love. I have been very fortunate to have my eldest brother, Arif Hossain, without whom there is no way I could have possibly accomplished this. I also want to mention my mother and father, Nazma Begum and Altaf Hossain, whose understanding of the value of education is indeed beyond my comprehension.

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LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
CANSIM	Canadian Socio-Economic Information Management System
CHIA	Health Informatics and Analytics
CKD	Chronic Kidney Disease
CKD-CP	Chronic Kidney Disease Clinical Pathway
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-SC	Chronic Kidney Disease-Specific Clusters
CMA	Canadian Medical Association
CORR	Canadian Organ Replacement Registry
CRMS	Client and Referral Management System
CSD	Census Subdivisions
Cys C	Cystatin C
DSR	Direct Standardized Rate
DSR,V	Direct Standardized Rate for Nephrologist Visits Frequency
eConsult	Electronic Consultation
eGFR	Estimated Glomerular Filtration Rate
ESKD	End-Stage Kidney Disease
FFS	Fee-For-Service
GBD	Global Burden of Disease

GFR	Glomerular Filtration Rate
GIS	Geographical Information System
GKHA	Global Kidney Health Atlas
GLMs	Generalized Linear Models
HRP	Human Research Participants
HTN	Hypertension
HVGB	Happy Valley-Goose Bay
IBM SPSS	International Business Machines- Statistical Package for The Social Sciences
KDIGO	Kidney Disease Improving Global Outcomes
KEEP	Kidney Early Evaluation Program
LMICs	Low-And-Middle Income Countries
MALU	Micro-Albumin Urine Test
MCP	Medical Care Plan
MDRD	Modification of Diet in Kidney Disease
MediTech	Medical Information Technology
NKF KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NL	Newfoundland and Labrador
NLCHI	Newfoundland & Labrador Centre For Health Information
OR	Odds Ratio

PCP	Primary Care Providers
PDAD	Out-Of-Province Discharge Abstract Database
PHRP	Protection of Human Research Participants
POR	Patient Oriented Research
RIHA	Regional Integrated Health Authority
RRT	Kidney Replacement Therapy
Scr	Serum Creatinine
TCPS	Tri-Council Policy Statement
TPMI	Translational and Personalized Medicine Initiative
UACR	Urine Albumin to Creatinine Ratio

Chapter 1: Introduction and Background

1.1 Introduction

Practicing nephrologists in Newfoundland and Labrador (NL) frequently suggest that kidney disease prevalence has increased over the past two decades.[1,2] Although this assertion is based on anecdotal evidence, if proven correct, it may have a significant impact on the future planning and development of kidney services in the province. The prevalence of chronic kidney disease (CKD) in NL needs to be identified while anticipating the needs for kidney care services throughout the provincial health care system.

1.2 The current structure of the provincial health care system

Newfoundland and Labrador is one of the provinces located as part of mainland Canada. The province is divided into four health authorities, namely Eastern, Central, Western, and Labrador-Grenfell regional integrated health authorities (RIHA). There are kidney care services in all four health authorities, ranging from travelling nephrology clinic to kidney replacement therapy (RRT). Although the best possible service is to have a full range of kidney care, it is not practical to deliver the kidney care service to every community because of the various geographic distribution of the relatively small population throughout the province. Nephrology services are therefore mainly centered

in St. John's and Corner Brook in the eastern and western health region, respectively, where the majority of the NL population lives. There are two nephrologists in Corner Brook, and the rest of the province's eight nephrologists are in St. John's. There are some travelling clinics providing nephrology services across the regions. There is also a well-established telehealth system in the province; it is used regularly during the dialysis unit follow-ups, but the kidney clinics do not often use it. There is an e-consult service available, but most of the nephrologists are not participating. This current structure of kidney service delivery limits patients' in-person follow-up, especially in central and Grenfell-Labrador health regions and other remote locations as well. Also, it often displaces patients and families to areas that offer appropriate kidney care services.

1.3 Chronic kidney disease

Chronic Kidney Disease (CKD) is defined as the presence of reduced kidney function and/or evidence of kidney damage for a period of three months or more.[3,4] Evidence of kidney damage includes albuminuria, abnormal pathology/radiology or reduced kidney function (an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2).[5] CKD has become a major public health challenge in the last decade due to its increased prevalence and strong association with kidney failure (end-stage kidney disease, ESKD).[6,7,8] According to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[9], CKD can be classified into the following six stages: G1-2, G3a-b, G4-5.

This KDIGO international system is a 2D matrix (Figure 1) that integrates the three levels

(A1-3) of albuminuria (urine albumin to creatinine ratio in mg/g or mg/mmol) and the

level of kidney function ((measured by either eGFR, or, measured GFR (mGFR)). The

matrix describes the risk stratification of the severity of CKD progressing up to ESKD. For

example, a patient whose eGFR is in the category of G3b (Moderately to severely

decreased kidney function) and whose albuminuria is severely increased (A3: >300mg/g

or >30mg/mmol), would be referred to as a CKD stage G3bA3, meaning he would have a

very high risk of progressing to kidney failure.[10]

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012			Persistent albuminuria categories Description and range		
			A1	**A2**	**A3**
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m²) Description and range	**G1**	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60-89	Green	Yellow	Orange
	G3a	Mildly to moderately decreased	45-59	Yellow	Orange	Red
	G3b	Moderately to severely decreased	30-44	Orange	Red	Red
	G4	Severely decreased	15-29	Red	Red	Red
	G5	Kidney failure	<15	Red	Red	Red

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

CKD=chronic kidney disease; GFR=glomerular filtration rate; KDIGO=Kidney Disease: Improving Global Outcomes

Figure 1: Risk stratification chart for prognosis of CKD by eGFR and albuminuria categories (figure adapted from original source, used with permission)[11]

1.4   CKD risk factors

One major cause of kidney function impairment is scarring or fibrosis of the blood vessels coiled within the glomeruli, a cluster of capillaries located inside the kidneys. The scarred vessels limit blood flow, and thus, the glomeruli cannot filter out waste products efficiently.[12,13] This scarring process is common in patients with high blood pressure[14] and diabetes[15], which places them at a higher risk for CKD. Diabetes, which is characterized by increased blood sugar levels, is caused by the body's inability to produce or use insulin, a blood glucose regulating hormone.[16] High blood sugar levels signal mesangial cells within glomeruli to produce scar tissue which then interrupts blood flow through the glomeruli.[17,18,19]

In hypertension, the increased blood pressure causes thickening of the afferent arteriole in order to withstand the pressure and this thickening narrows the arteriolar lumen. As the lumen narrows blood and oxygen flow lessen causing ischemic injury to the nephron's glomerulus. Immune cells like macrophages and foam cells enter the damaged glomerulus and stimulate the production of transforming growth factor beta1. This growth factor causes mesangial cells to convert into mesangioblasts, the more immature stem cell state of mesangial cells. Mesangioblasts secrete extracellular structural matrix. Excessive extracellular matrix causes hardening and scarring of the glomerulus known as glomerulosclerosis, which limits the nephron's ability to filter the blood and leads to chronic kidney disease over time.[20]

Fifty percent of all diabetic patients[21] and ~20% of hypertensive patients[22] worldwide are estimated to develop CKD during their lifetime. More than 75 percent of all cases of stage 3-5 CKD in Canada are attributable to these two diseases.[23] Other common risk factors such as obesity, cardiovascular disease and family history of end stage kidney disease also contribute to higher risks for CKD.[24]

1.5   CKD biomarkers

The two essential laboratory measures necessary to diagnose CKD clinically are urine albumin to creatinine ratio (UACR) and the estimated glomerular filtration rate[25] The UACR which measures albumin excretion, can be measured using a spot urine test (preferably from the first-morning void). A UACR exceeding >30 mg/g indicates albuminuria, which is one of the strongest predictors of declining kidney function.[26] It has been recommended that UACR should be tested annually in all patients with type2 diabetes and patients who have had type 1 diabetes for five years or longer.[27]

Another important test for identifying CKD is eGFR. For patients who are clinically stable and non-hospitalized, eGFR is considered the best indicator to measure kidney function.[28] As serum creatinine (Scr) is the primary component of the eGFR measurement, there are numerous formulas that exist to calculate eGFR by using Scr.[29] One of the most widely used formulas is "The Modification of Diet in Kidney Disease"

(MDRD) equation, which encompasses data including age, sex, race, and serum creatinine.[30]

$$\text{eGFR}_{MDRD} = 186 \times (S_{cr}/88.4)^{-1.154} \times \text{Age}^{-0.203} \times [1.21 \text{ if Black}] \times [0.742 \text{ if Female}]$$

(where, Scr = serum creatinine in μmol/L)[31]

The standard equation is applicable to male Caucasians and has an adjustment for females and black individuals. For females, the equation multiplies the GFR estimates by 0.742. This is because average muscle mass and creatinine generation rate in women are lower relative to men. Also, for black individuals, the equation will multiply the eGFR estimate by 1.21 due to the fact that black individuals have higher average muscle mass and creatinine generation rates compared to Caucasians.[31]

Although the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) recommended eGFR$_{MDRD}$ in CKD due to an accuracy of 92% of values being within 30% of true GFR[32], the grading of CKD should also be based on whether the UACR is more than 30mg/g creatinine or the eGFR is less than 60 ml/min/1.73m2 on two separate occasions tested three or more months apart.[33] Another widely used creatinine-based equation is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[34] When eGFR value is anticipated to be >60 mL/min/1.73 m², this recently formulated equation provides more accurate results.[35]

As alternatives to creatinine-based equations, a number of researchers have proposed GFR estimates based on other molecules such as cystatin C (Cys C), which is less influenced by muscle mass than serum creatinine. It provides an index of the glomerular filtration rate, especially in population subgroups including very obese, elderly, malnourished, vegetarians, etc. in whom serum creatinine may be inconsistent.[36]

CKD may not be identified based on a single or isolated UACR or eGFR measurement.[37] Age[38], along with, kidney function stability[39] play an important role in an inconsistent eGFR reading. Many health conditions may present with fluctuating serum creatinine levels, which may lead to the under or overestimation of eGFR.[40,41] Hospitalization[42], acute kidney injury (AKI)[43], major limb amputation[44], hepatic cirrhosis[45], and severe obesity[46] are among such health conditions. False positive results may also be seen in both very young and old age groups.[47] Thus, the eGFR test for CKD may not always be accurate and limitation free.[48]

1.6   Prevalence of CKD

1.6.1   Global trends

There has been an alarming increase in the prevalence of CKD globally. In 2015, there were 1.2 million deaths due to CKD worldwide compared to 0.93 million in 2005, a 31.7% rise in 10 years (95% CI 27.7-35.6; p<0.05). The estimation of 1.2 million deaths

due to CKD by the Global Burden of Disease (GBD) study in 2015 makes it the 17th leading cause of death, up from 21st in 2005 and 25th in 1990.[49] Accounting for the shifting age structure of the global population, by contrast, the rise of age-standardized death rates due to CKD was only 1.2% (95% CI -1.9-4.0; p>0.05).[49]

The Studies indicated that the global mean CKD prevalence in females [14.6% (12.7-16.7%)] was more common than in males [12.8% (10.8–11.9%)], irrespective of CKD stages[50], possibly due to the global increase in sex-related differences in obesity[51], and other contributing factors such as high blood pressure[52] and diabetes mellitus[53].

According to the Global Kidney Health Atlas (GKHA)[54] project, survey from 125 countries (93% of the global population) showed that CKD was common throughout the world: 7% of the total population in South Asia, 8% in Africa, 11% in North America, and 12% in Europe, the Middle East, East Asia and Latin America. It is more common in high-income countries: 24% in Belgium and Saudi Arabia, 18% in Poland, 17% in Germany, 16% in UK and Singapore, and 14% in the USA, with the exceptions of Norway and the Netherlands at only 5%, than low-and-middle-income countries (LMICs). However, a disproportionate increase in CKD prevalence rates was seen in LMICs as well.[55] The fastest CKD prevalence rate increase has also been seen in LMICs (especially Asia and Africa), where most people with CKD are likely to live and where the annual prevalence rate of CKD related death has increased by 5% from 1990-2013.[56] The increase in CKD prevalence rates in developing countries follows the trends of urbanization and lifestyle

changes, including increasingly sedentary lifestyles, less physically demanding work, and the global nutrition transition which is marked by increased intake of energy-dense but nutrient-poor foods (often high in sugar and saturated fats).[57,58,59]

The number of people with CKD is increasing around the world. In the USA, if the current trend continues, it is projected that the prevalence of CKD (in adults ≥30 years) may increase from its current rate of 13.2% to 14.4% by 2020 and 16.7% by 2030. Furthermore, for adults aged 30-49, the remaining lifetime incidence of CKD is 54%, suggesting more than half of the adult population will have CKD in their lifetime.[60] However, fortunately, CKD is largely preventable; for example, for diabetic patients, controlling blood sugar can help to prevent the onset of early-stage CKD.[61]

1.6.2   The Canadian perspective

The Kidney Foundation of Canada estimates that 1 in 10 Canadians has kidney disease. The Foundation also reports that millions of individuals are at risk of kidney disease according to a 2016 annual report. CKD prevalence has increased tremendously over the past two to three decades in the Canada.[62]

According to the results of a nationally representative heath measures survey (2007-09), approximately 12.5% of the Canadian population is affected by CKD.[23] Arora et al. found that about 2.9 million Canadian adults were living with stage 3-5 CKD. The prevalence of CKD is markedly higher (31%) in those aged 65 or older. The most

common causes of CKD are diabetes and high blood pressure followed by other health conditions and kidney diseases. Elliot et al.[63] note that the majority of patients with CKD are treated in primary care settings. The remaining relatively small number of severe cases are seen by nephrologists.

1.6.3 Prevalence of CKD in the Indigenous population

Studies have shown that the Indigenous population suffers from increased risk of undiagnosed and untreated CKD compared to non-Indigenous population.[64] In Indigenous communities, the prevalence of severe CKD was almost two-fold higher compared to non-Indigenous population.[65,66] In Australia, research has shown that Indigenous people can be as much as 3-4 times more likely to have CKD than non-Indigenous people.[67] In native Australian communities, CKD may begin two or three decades earlier, without diagnosis; therefore, people who are diagnosed with CKD at middle age and have developed ESKD, essentially started developing CKD during their childhood.[68]

In the last two decades, the prevalence of CKD among Indigenous populations in Canada has increased dramatically.[69] In addition, the prevalence of CKD-related complications, such as ESKD, is 2 to 4 times higher when compared with non-Indigenous people.[70,71]

1.7   Adverse consequences of CKD

CKD can lead to end stage kidney failure. In the last twenty years, the number of

Canadians being treated for kidney failure has more than tripled. In Newfoundland, the

rates for kidney replacement therapy (RRT) for kidney failure patients in 2013 were

highest among all other provinces. Dialysis costs $56,000-107,000 per patient per year,

meaning that the Canadian healthcare system expends around $2.5 billion annually for

dialysis patients.[72]

Both CKD and its treatment can take a great physical and psychological toll on

individuals and families. Hemodialysis may take up to 5 hours a day and 3 times per

week. On the other hand, although there are long waits and high initial costs, kidney

transplantation may save the healthcare system over $250,000 per patient in dialysis

costs over five years.[73]

1.8   Kidney care delivery

1.8.1   When should a patient be referred to a nephrologist?

As the literature has shown, timely referral to a nephrology consultation delays

CKD progression[74], improves clinical outcomes[75,76] and minimizes overall costs[77]. When

there is no albuminuria present, the optimal time for this consultation occurs at CKD

stage 3b when eGFR falls below 45 mL/min/1.73m^2.[37,78] Other important factors to

consider in order to determine when a referral should be made include electrolyte

imbalances, uncontrolled hypertension, metabolic abnormalities, urinary abnormalities,

and anemia.[79] One quantifiable indication that may prompt the family physician to refer a patient for a nephrology consultation is a decline in the baseline eGFR at a rate equal to or greater than 5 mL/min/1.73m^2 per year.[80] A primary care provider might also seek an early nephrology consultation for those with diabetes and hypertension in patients showing any signs of hematuria, persistent proteinuria, or micro/macro-albuminuria in two consecutive urine tests at least 3 months apart.[81]

A primary care provider can also enhance patients' baseline knowledge of CKD with applicable CKD management guidelines and education.[82] In patients with CKD and diabetes, management is mostly subject to a patient's behaviors.[83,84] Early intervention with high risk patients also means implementing patient-centered education for chronic disease management. Timely diagnosis of high-risk patients along with prompt intervention and patient-centered education not only slows the progression of CKD but also improves outcomes.[85]

1.8.2   Stable and progressive CKD

Kidney care accounts for a substantial amount of healthcare spending in Canada.[86] To control the ever-increasing expense of kidney-care, researchers and policy makers have focused on the delivery of nephrology services as a way to regulate costs.[87] In Canada, over 2.9 million citizens have CKD at stage 3 or higher, meaning that their kidneys are functioning below or at approximately 60% of their normal capacity.[50] Among them, only a small number of patients are treated by nephrologists, with the

clear majority seen by a family physician in a primary care setting.[88] Some of the CKD

patients from both groups decline rapidly, their kidney function steeply deteriorates,

and they need dialysis and/or a transplant in the end. However, in most cases, kidney

function remains stable for years.[89] Stable kidney function occurs when the level of

eGFR decline is within the range of 1-4 ml/min/1.73m^2 for 3 consecutive tests. This is

opposed to progressive kidney function decline, which is referred to as

>=5ml/min/1.73m^2 decrease of eGFR per year.[90] Physicians are often unable to

recognize progressive kidney dysfunction, leading to late referrals and lost opportunities

to slow kidney function decline.[26,91] It is expected that kidney function will remain stable

in patients who have stable kidney function irrespective of CKD stage and who are

managed in a kidney care program. Their kidney function may not improve but it will

usually not deteriorate either. On the other hand, with proper nephrology service

delivery, it is possible to slow the rate of kidney function decline for some patients with

a history of declining kidney function.[92] For these patients, the regression of

glomerulosclerosis may prolong the time before the onset of ESKD and its management

and thus improve outcomes.[93]

1.8.3   Early recognition and management of CKD

A systematic approach to diagnosing CKD early is crucial. Simple blood and urine

tests may identify most patients who are at an early stage of CKD. The National Kidney

Foundation of America, through their Kidney Early Evaluation Program (KEEP), offers

free urine testing to all adult high-risk individuals with diabetes, HTN or family history of kidney failure to address kidney problems.[94] Thus, just after detection, it is important to start renoprotective treatment immediately, not to cure CKD, but to slow down the deterioration of kidney function. This may also prevent complications arising from kidney disease, such as premature stroke or heart attacks, as well as progression to ESKD.[3] By using both the administrative data and the health-related information with laboratory data, it has been shown that a simple urine test (the amount of protein in urine) is one of the most important predictors of the progression of chronic kidney disease.[95] It is much easier to make informed choices about treatment options when CKD is detected early. And, if CKD progression is being well taken care of from its early stages, the prevention of ESKD is more likely.[96]

1.8.4 Addressing the gaps

The overall lifetime risks for CKD stage 3a (eGFR> 45 mL/min/1.73m^2) from birth is estimated at 59%. The likelihood of more severe CKD is lower, for example the risk is 3.6% for CKD stage 4 or more.[97] So, recognition of CKD is vital, like recognition of diabetes and high blood pressure. Kidney function does decrease with age. Urine protein, which is a marker of kidney damage, needs to be on the list of lab tests for individuals who are at risk. People need to have a standard awareness of kidney disease parallel to the understanding of diabetes and hypertension that has existed for years.

Existing CKD awareness is low.[98] Stage 4 CKD is present when kidney function is

about one quarter of normal, yet only half of those who currently have severe kidney

disease (CKD stage 4 or worse) are diagnosed. It is important to recognize what CKD is,

detect it early, focus on the specialized treatment required, and reduce complications.[99]

A study of CKD patients in Alberta determined that the chronic kidney disease

clinical pathway (CKD-CP) online tool for primary care providers (PCP) greatly increases

PCP's ability to diagnose, manage and refer CKD patients and thus reduces evidence-

practice gaps in the primary care setting.[100]

1.8.5   Kidney care service delivery in remote communities

In Canada, we have a health care system that triages people based on

community to substandard care. There is a lack of access to kidney care services for

people in remote areas which acts as a significant barrier to maintaining health.[101] These

barriers or challenges include but are not limited to healthcare professional shortage[102],

lack of access to kidney care[103], long-distance travel to a kidney care facility[104], and poor

communication infrastructure for telehealth and e-consult[105]. The population in the

remote communities face inadequate kidney care services compared to their

counterpart living in close proximity to a health care facility.

1.8.6   Kidney care service delivery in Indigenous communities

For the Indigenous population, especially for those living in remote locations, a

major challenge is access to kidney care. Early diagnosis is important, but the distress

involved with leaving the community/reserve to receive appropriate kidney care must

be considered.[106] On top of the stress associated with traveling for medical care, they

also have very limited access to proper kidney care, amid a much higher prevalence rate

of CKD, and this therefore creates a burden on the available resources.[107] When

compared with the non-Indigenous population, the likelihood of kidney transplantation

for Indigenous people is only about one-third (hazard ratio=0.34).[71]

1.9   Patient oriented research (POR)

Engaging, listening to, and involving patients as partners in the research process

enhances the impact and quality of research in a variety of ways. It ranges from

formulating novel research questions, to taking new and interesting directions based on

patients' vast and diverse experiences. Engaging patients in this way is becoming a core

component of some medical research.[108] Patient oriented research (POR) can be

instrumental in creating a framework that allows researchers to share their vision,

interest, and concerns about research with the broader community. Through POR,

researchers can interact and reach out to the widest possible audience. Increased

awareness of societal needs is one among many potential benefits when researchers and patients work together and define research strategies for a specific project.[109]

The provision of integrated care is one feature of healthcare systems. There are many varying definitions for integrated healthcare in the literature. Common elements include: being patient-oriented, continuous delivery of healthcare, including healthcare research, and coordination between services.[110] Unfortunately, in many instances, limited patient oriented research within healthcare services leaves a gap in integrated healthcare. This gap leaves many patients unaware of available advanced kidney care, whilst healthcare professionals miss the opportunity to listen to patients' voices on healthcare deficits.[111] The research inquiries and objectives that are important to patient partners are very different than the ones that researchers think are important. Incorporating the patients' voice in all aspects of research is a key motivating factor in any population-based epidemiological research. Patients can ask questions, and be a part of the study design; their engagement is not limited to study participation, but also to looking at the results, interpreting the findings, and coming out with the best possible ways to disseminate these findings. All this makes the patient population the core of patient oriented research.[112]

1.10   Research objectives

a.   To determine the distribution of chronic kidney disease in the Newfoundland and Labrador health regions, and how this distribution varies in particular subgroups characterized by region of residence, age, sex, presence of diabetes, progression of kidney disease, and residence in communities with more Indigenous people.

b.   To determine the current status of CKD referrals and follow-ups by nephrologists in the province and across regions, for the same subgroups.

Chapter 2: Methods

2.1   Settings

Newfoundland and Labrador centre for health information is a custodian for provincial health data. Provincial health information standards for demographic, administrative, and clinical data are set by the Provincial Health Information Management Leadership Committee. The purpose of this standard is to ensure accurate and complete demographic and administrative information, a fundamental for valid and accurate patient identification. The information is collected within health care services at the point of patient registration/admission through standardized registration processes. Medical information technology (MediTech), the Client and Referral Management System (CRMS), Medical Care Plan (MCP), Vital Statistics, the Pharmacy Network, and Med Access (the provincial EMR) are among the registration modules from where the information flows into the provincial Client Registry for use by health care providers and other stakeholders, i.e. researchers. NLCHI maintains the Client Registry, which contains data including demographic information (name, address, date of birth) and administrative information (date of birth registration, MCP number, etc.). It allows accurate individual identifications by linking person-specific information from clinical information systems to the correct person. For laboratory specimens (e.g., blood/urine sample), laboratory staff enter lab results into MediTech while ensuring accuracy.[113]

Health data are being increasingly used in Canada.[114] Although privacy is a major concern while disclosing public health information for secondary use, there is a growing demand for health data for public health research, and policy-making purposes.[115] For that, high-quality data not only plays a vital role in providing objective information for study analysis but also helps in sound public health decision making. According to the University of Victoria eHealth observatory's electronic medical records data quality evaluation guide[116], a key characteristic of quality data is whether the data capture the same set of names for the same set of analytical variables. In NL, different health regions enter kidney function data by using different names for eGFR. Such inconsistency in kidney function test-results may impact clinicians' ability to recognize and compare test results in a shared care situation. It may also affect practice reflection, an essential element for quality data, where health data is used. To negate such impact, NLCHI provided practical approaches to maintain the quality of data by identifying different eGFR test names (for example: EGFRCALC, EGFRC, GFRPMDRD, etc.).

This retrospective cohort study was constructed by extracting records from the following data sets: the Medical Care Plan (MCP) database, the MediTech Laboratory database, the NLCHI Diabetes Database, the Canadian Organ Replacement Registry (CORR), NLCHI's Out-of-Province Discharge Abstract Database (PDAD), the Canadian Socio-economic Information Management System (CANSIM) database, and the CanMap® Six Digit Postal Code v7.2 database.

For the purposes of determining CKD prevalence and to see where and when specialist care was received, linkage had been made at NLCHI between the MCP claims database for nephrologists in NL and the Meditech Laboratory Database. The Diabetic registry data set was used to identify all patients with diabetes and the proportion of these patients that has been tested for CKD. CKD patients who were on dialysis or have had a kidney transplantation were identified and excluded by using the CORR data and PDAD, respectively.

In this chapter, the sources of the individual datasets used are reported, the characteristics of the variables used to analyze the data are discussed, and the methods used to analyze the data to address the study objectives are illustrated.

2.1.1 MediTech laboratory data

This includes records extracted from Regional Integrated Health Authority's (RIHA) MediTech Systems' Laboratory modules. Extracts were provided to NLCHI by each RIHA and include administrative, demographic and clinical information related to the laboratory tests performed in provincial facilities. The data (N=40,465 individuals) were used to identify all adult ($\geq$18 years of age) chronic kidney disease (CKD) cases. **Cases were identified by the study <u>operational definition</u> as individuals with CKD by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 on at least two occasions, at least 3 months apart[117], at some point of the study period between April**

1, 2011 and December 31, 2015. [Please note – Laboratory data from January 1, 2011-March 31, 2011 was not available due to quality issues identified by NLCHI Health Analytics and Evaluation Services Department during extraction].

While albuminuria is a key feature that can also identify and grade CKD, this was not used in our study as a minority of cases had urine albumin measured.

Characteristics of the variables from this database that are used in the study are described below.

Patients' study ID: A study code unique identifier is tabulated for each patient, named the 'Study ID'. This allows the data to be de-identified for the analysis.

Age: (NLCHI-derived): Age was determined to be incorrect in the source data (MediTech Laboratory Data) in the data validation process. The age information file was thus replaced with age-derived from the 2016 MCP Beneficiary Registry information (see section 2.1.2) to maintain the integrity and validity of data. Derived-Age in years was calculated based on the simple subtraction of the patients' birth year from the laboratory test date.

Gender: Male and female.

Kidney function test: Each health region/facility utilized different names for the same or similar tests for kidney function. In the original data, both serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) tests were

provided. Serum creatinine test results were later transformed into eGFR by using the Modification of Diet in Kidney Disease (MDRD) formula described earlier.[31] CKD measured by eGFR$_{MDRD}$ with the clinically relevant cutoff values between 5-120 ml/min/1.73m^2 was considered and any patients with eGFR below 5 ml/min/1.73m^2 or above 120 ml/min/1.73m^2 were eliminated from the data.

Not every eGFR from the same patient was below 60 ml/min/1.73m^2 either before or after the period when they were identified. This is the working definition of CKD based on how it is applied by the NLCHI data analyst. The CKD is recognizable once the eGFR is below 60 ml/min/1.73m^2 and stays there for three months, but this does not require that a physician has diagnosed the patient as having CKD. Therefore, some eGFRs appeared to be high and others appeared low within the study period. A choice has been made to cut-off the data when the eGFR were much too high or much too low to be clinically believable. This is because it is unlikely that these values represent a correct eGFR value.

Values of eGFRs >120 ml/min/1.73m^2 are not plausible values. This means that there must be something erroneous either in the data, or in the creatinine assay. Heavily built patients in general may have a high eGFR, but this does not make medical sense where there is an eGFR over 120 ml/min/1.73m^2.

And moreover, the study focuses on people with CKD where an eGFR over 120 ml/min/1.73m^2 was really not relevant. For this reason, eGFR values over 120 ml/min/1.73m^2 were left out from the analysis.

Very low eGFRs (<5 ml/min/1.73m2) were also left out. However, the study may include some dialysis patients, who are not registered with CORR, or patients who did have a very low eGFR at some point for various reasons such as acute kidney injury, for example. And again, the study focuses only on CKD patients, not dialysis patients.

History of diabetes mellitus: Derived variable- based on linkage to NLCHI Diabetes Registry- indicates presence of patient records/information on diabetes in the Provincial Diabetes Registry. Patients with 'Yes' indicates the presence of diabetes and 'No', indicates the absence of diabetes.

To be considered a diabetes case in the Provincial Chronic Disease Registry, an individual must meet the following criteria:

- Identified as a diabetes case in the Canadian Chronic Disease Surveillance System (CCDSS): The diabetes case definition used by the CCDSS is one hospitalization or two or more physician visits with a diabetes diagnosis code (250 in ICD-9; E10-E14 in ICD-10) within a 2-year period. While identifying individuals for diabetes from primary

care charts, this case definition has shown 86% sensitivity and 98% specificity.[118]

OR,

- Any two of the following test results in a two-year period:

    o Fasting Plasma Glucose test result of ≥ 7mmol/L, OR

    o Hemoglobin A1C test results of ≥ 6.5%, OR

    o 2-hour Plasma Glucose in a 75g Oral Glucose Tolerance Test result of ≥ 11.1 mmol/L, OR

    o Random Plasma Glucose test result of ≥ 11.1 mmol/L.

Date of laboratory tests: Laboratory test dates were entered based on the Meditech Collection date for every test throughout the study period from April, 2011, to December, 2015.

Postal code information: Geographic information was based on six-digit postal codes taken from the 2016 MCP Beneficiary files (see section 2.1.2). The postal code indicates the patients' place of residence in 2016.

2.1.2 MCP fee-for-service physician claims data

The MCP is an overall medical care insurance plan intended to cover the physicians' service fee. The master database from the provincial MCP program of the Department of Health and Community Services is the primary source for MCP data. This

Registry based data is managed by NLCHI and consists of clinical, administrative and demographic information on patients' eligibility for provincial MCP services. The data has 3 different files, namely the beneficiary registry, provider registry, and fee-for-service (FFS) physician claims. The population size was 8,850 individuals in this database.

The MCP Beneficiary Registry includes demographic information about individuals insured by the program and is a 'snapshot' of registrants' information at a point in time, usually December 31 of a particular year. The person-specific health care number issued at the time of registration is also included.

The Provider Registry includes demographic and licensing information about physicians registered to submit claims for services under the Newfoundland Medical Care Insurance Act. A unique identifier is provided to registrants for billing purposes.

The Fee-for-Service (FFS) Physician Claims dataset includes clinical and other information about services claimed under the Newfoundland Medical Care Insurance Act. Date of service, place of service, and diagnostic and fee codes used to describe procedures/services performed are included.

Patients who were residing as a permanent resident outside Newfoundland and Labrador were excluded. Residence outside NL was determined using MCP registry information.

The medical licensing body is inconsistent in who they label as nephrologists. Part of this is historical – some were in practice before the Royal College recognized the

subspecialty. Some more recent ones may have been certified in the US and listed as a nephrologist by Credentials committees in the RIHAs. We invited all practicing nephrologists in NL seeking permission to use their visit data for the study [see Appendix A]. There were transiently also other nephrologists, who saw some nephrology cases but a lot of non-nephrology cases, so we left them out from the study. In terms of which physician visits we wanted to capture, this would essentially be visits to physicians who practice Nephrology. This excluded visits to internists per se even though a couple of those were listed as "Nephrologists" by the College, they were not credentialed to provide nephrology care. There are internists at Grand Falls who do provide dialysis, but they don't do pre-dialysis CKD care which is the focus of this study, so their visits were not captured either. Eight nephrologists are practicing based on the city of St. John's in ERIHA and two nephrologists are practicing in Corner Brook in WRIHA. A couple of nephrologists from ERIHA travel periodically to CRIHA and LG-RIHA.

The following is the list of variables from this database that were analyzed.

Patients' Study ID: The same unique identifier as that of the MediTech laboratory data was used for CKD patients who had been seen by nephrologists.

Nephrologist Visits: This was a derived variable based on the linkage with MCP FFS physician claims data. The variable denoted the count of visits with a nephrologist per CKD patient. All nephrologist visits throughout the study periods were taken into account. All nephrologists are fee-for-service and submit

claims. After the study period started, the first nephrologist visit was identified and then all subsequent visits were counted.

Nephrologist Visit Date: Based on all service dates of nephrologist visits per CKD patient throughout the study period.

Nephrologist Visit Location: RIHA location of nephrology service was recorded based on the most recent date of nephrologist visit.

Postal Code information: The six digit postal code of CKD patients' place of residence was extracted from the MCP Beneficiary file.

2.1.3 The NLCHI diabetes database

The database includes records for all residents of Newfoundland and Labrador who have been diagnosed with diabetes as recorded in provincial clinical information systems. The NLCHI Diabetes Database was used to identify all prevalent cases of diabetes between January 1, 2011 and December 31, 2015. Patients with 'Yes' indicates the presence of diabetes and 'No', the absence of diabetes. The presence/absence (Yes/No) of micro-albumin urine test (MALU) was provided. It was used to detect kidney damage in diabetic individuals who are at risk of developing CKD. The population size on this database was 76,692 individuals.

2.1.4 The Canadian Organ Replacement Registry (CORR) and NLCHI's Out-of-Province Discharge Abstract Database (PDAD)

CORR collects data from hospital dialysis programs, regional transplant programs, organ procurement organizations, and kidney dialysis services offered at independent health facilities. Patients are tracked from their first treatment for end-stage organ failure (dialysis or transplantation) to their death, unless they are lost to follow-up. CORR data were linked at NLCHI and used to exclude patients on dialysis. Patients with 'Yes' indicated for Peritoneal/Hemodialysis were identified as dialysis patients and were excluded. Patients who have dialysis for acute kidney injury are not captured by the CORR data, and as such may have been included in the cohort.

With respect to the transplant data, all NL kidney transplants were performed out of province (most were performed in Nova Scotia). The data submitted to CIHI were considered to be under the custodianship of the submitting province. Therefore, CORR provided no transplant data. Patients who had a kidney transplant were therefore identified and excluded using NLCHI's Out-of-Province Discharge Abstract Database.

2.1.5 Canadian Socio-economic Information Management System database:

(see Appendix B)

Canadian socio-economic information management system is Statistics Canada's main socioeconomic time-series population database consisting of the number of

people living in a health region by age and sex. NL health regions are based on

administrative boundaries defined by the provincial ministry of health according to

provincial legislation. CANSIM was used for computing age-standardized and age and

sex-specific CKD prevalence rates in different NL health regions from 2011 to 2015.[119]

2.1.6   The CanMap® Six Digit Postal Code v7.2 database

In order to effectively map each study ID's location to each health authority, six digit

postal codes were used. The CanMap® 6 digit postal code database contains the most

precision-based points representing addresses across Canada. The database is produced

by DMTI Spatial, a Digital Map Products company (a private company that creates the

CanMAP geographic information system (GIS) Data used by the federal

government/universities). The CanMap file also includes the Canada Directory which

contains provincial boundaries, regional municipality boundaries, area code boundaries,

and the 1996 census subdivisions (CSD) boundary data. The postal codes are

subsequently mapped to regional municipality boundaries (communities) and then

regional health authorities. Finally, latitude and longitude coordinate points were used

to locate different communities on the map.

Data for study cases were arranged in an SPSS data file and then imported to the

GIS-based mapping software, 'Tableau'. Specific communities belonging to their

Individual cases were represented on the map, according to their postal code

information. The coordinate (latitude and longitude) locations of the communities of the CKD population were derived from the postal codes provided for each patient in the Meditech Laboratory and the MCP Fee-for Service Physician Claims databases. Coordinates that were not recognized by the CanMap® Six Digit Postal Code v7.2 database were manually inserted into the Tableau software after online Google search of the postal code specific to the community. The display of communities on the map was then pointed out by dots.

To ensure that the privacy of the patients included in this study was not compromised as a result of analyzing the 6 digit postal code data, the rule of five method was used to prevent any re-identification of patients through spatial information. Any sub-region or aggregate that had less than five patients was merged with an adjacent sub-region or aggregate so that none of the areas being analyzed had less than five patients. This process is widely used as a method to prevent the re-identification of patients through spatially referenced data.

2.2 Study design

This is a retrospective cohort study to establish CKD prevalence and to understand kidney care delivery service across different health regions of NL. This study also utilizes the GIS mapping that helped visualization of people living in the remote communities with the burden of CKD.

We were able to look at the number of people in the broader municipal communities within each health region. For reasons of privacy and confidentiality, we could not identify people in very small communities. It is NLCHI policy not to identify individuals within groups of smaller than 5 people with CKD. Since we cannot analyze the very small communities because of the limitations of the policy, we choose bigger sites of CKD population (thirteen communities) for comparative analyses. The differences in the proportion with CKD between the larger communities (namely St. John's region, Carbonear, Burin, Clarenville, Bonavista, Gander, Grand-Falls-Windsor, Corner Brook, Stephenville, Port-aux-Basques, St. Anthony, Happy Valley-Goose Bay, Labrador City) were compared. Four health regions were compared first in terms of the proportion with identifiable chronic kidney disease and then broken down within the regions into specific communities.

2.3   Research team

A multidisciplinary research team, with varying expertise and skill sets, was introduced because of the varying nature of the study. The research team consists of a master's student [Dr. Mohammad Akhtar Hossain] from the department of clinical epidemiology as a principal investigator, one professor of medicine (nephrology), Dr. Brendan Barrett, as a supervisor, two associate professors of medicine (nephrology), Drs. Sean Wilson Murphy and John Shik, as co-supervisors, and a research coordinator

[Oliver Hurley] from the faculty of medicine. The expertise of this research team included research design, data analysis, geographic information system analysis, kidney disease, and biostatistics. I was responsible for various stages of research design including but not limited to protocol writing, study design, data screening/cleaning, data analysis and report writing. I was further supported by three co-investigators (patients or related to patients: Ms. Kim Hickman, Ms. Carla Thompson and Ms. Trina Ralph) as part of the patient oriented research.

2.4   Research environment

This study was carried out within the Clinical Epidemiology Research Unit at the Memorial University of Newfoundland. It had the necessary infrastructure [e.g. adequate space, equipment (a desktop with the necessary software including Microsoft office and statistical package [International Business Machines- Statistical Package for the Social Sciences (IBM SPSS)], and facilities (i.e. conference space, projector etc.)], to conduct this research study, including access to the Memorial University of Newfoundland Health Science library for access to the current literature.

2.5   Study population, inclusion, and exclusion criteria

All patients with identifiable chronic kidney disease (see operational CKD

definition, page 37) at the various Newfoundland and Labrador health regions between

April 1, 2011, and December 31, 2015, were included in the study.

2.5.1   Inclusion criteria

Age ≥ 18 years

Identified CKD patients based on laboratory criteria

Diabetic patients aged ≥18 years

2.5.2   Exclusion criteria

Patients who were on chronic dialysis

Patients who have had a kidney transplantation

Patients who were residents outside Newfoundland and Labrador

(NLCHI did not report the number of people excluded because of dialysis

and transplantation)

2.6   Data analysis in the Indigenous population

There was an interest from patient partners in looking at any differences

between Indigenous and non-Indigenous people with CKD in Labrador-Grenfell Health

region. We do not have data to assign the Indigenous status of individuals; as such, we

are using the coastal community with majority Indigenous people as a proxy. These

coastal communities with CKD (namely, Cartwright, Charlottetown-Labrador, Hopedale,

Makkovik, Mary's Harbour, Mud Lake, Nain, Natuashish, North West River, Port Hope

Simpson, Postville, Rigolet, and St. Lewis) have a majority (>80%) Indigenous

population.[120] [Appendix C] Therefore, to determine whether or not there is a difference

between Indigenous and non-Indigenous communities, we use these coastal

communities as an approximation of an Indigenous population. Thus, the proportion of

CKD patients within the Labrador coastline communities reflects the CKD prevalence in

the Indigenous population rather than in the Caucasian population. We use this proxy

measure as individuals are not identified as Indigenous or not in the dataset.

2.7   Sample size calculation

As all patients' records, available and documented in the NLCHI registry, were

included in the study design for the selected study period of April 2011 to December

2015, sample size calculation was not necessary to conduct this retrospective

observational study. However, as our primary objective is to establish CKD prevalence,

we only need 3,457 CKD with 95% confidence interval based on the following formula of

sample size calculation for prevalence study.[121]

$$n = Z^2 \times P (1-P) / d^2$$

where,

n = sample size,

Z = 1.96; Z-statistic for a level of confidence,

P = expected prevalence or proportion (in proportion of one; here, national CKD

prevalence of 10% was used, P = 0.1), and

d = precision (in proportion of one; in this case 1%, d = 0.01).

Thus, a sample size of 3,457 would provide 95% confidence with 1% absolute error in

the estimated prevalence of CKD among the NL population. We based our calculation

here on knowing that we would have sufficient cases to identify the prevalence.

2.8   Patients' engagement

To facilitate the process of patient-oriented research, three patient partners

were invited, by email notification [Appendix D], at different phases as the study moved

forward. These phases include: a) inclusiveness: patient engagement was blended with

patients' perspectives, cultures, and their kidney care experiences; b) initial protocol

writing phase: we held a meeting with these patients, participants were asked to review

the research proposal and for any new ideas to add or gather feedback on already

existing information; c) research outcome phase: requested interpretation of results; d)

knowledge translation phase: asked patients partners to help share the research

outcomes.

2.9   Data analysis

Descriptive analyses were used to calculate the prevalence. The prevalence was

reported as percentage (%). For descriptive purposes, patients' kidney function

measured by eGFR was categorized as such: <60 (45-59), <45 (30-44), <30 (15-29), and

<15 (5-15) ml/min/1.73m^2. Individuals were grouped into five age categories (18-39, 40-

49, 50-59, 60-69, and 70+ years) based on their age at baseline (2011).

We determined CKD prevalence in a number of steps. First, we considered the

proportion of CKD patients in different RIHA communities by age group for each year of

the period 2011-15. Then, we looked at the proportion of the CKD population who were

and were not seen by a nephrologist. We also examined the influence of factors (age,

sex, diabetes, health region, CKD stages, and kidney function stability) on the frequency

of nephrologist follow-ups. And finally, we documented CKD among the Indigenous

communities. The following chart (Figure 2) shows all components of analysis followed

in this study.

| MediTech Laboratory Database | MCP Fee-for Service Physician Claims Data | The NLCHI Diabetes Database | CORR and PDAD | CANSIM Database | CanMap® Six Digit Postal Code v7.2 Database |

NL CKD data

Analytical Components

- Distribution of CKD across RIHA communities by age, 2011-15

- Distribution of CKD RIHA communities by level of eGFR, 2011-15

- Distribution of CKD in NL by stage in relation to age, sex, and diabetes status

- Frequency of eGFR measurements

- Nephrology visits across patients' demographics and clinical characteristics

- Association between nephrologist visit and patients' demographics and clinical characteristics

- Kidney care delivery

- Direct age-standardized rate for nephrologist visits

- Factors influencing the frequency of nephrologist follow-ups

- Status of referral to a nephrologist for CKD patients

- Proportion of CKD patients receiving nephrology service within their own region

- Distribution of CKD in Indigenous community

- Proportion of people with diabetes tested for CKD

Figure 2: Study analytical approach.

The differences between how often a patient receives follow up services within different communities and health regions were measured by the frequency of laboratory tests and nephrologists' visits. Frequent lab tests influence the likelihood of identifying CKD and also reflect the adequacy of care.[122] Depending on the prior laboratory findings, it is important to look at differences in the frequency of blood work at varying degrees of kidney function for CKD patients. Also, to assess the degree to which current nephrology service delivery matches the apparent needs, the study compared follow up frequency for CKD patients by the number of nephrologist visits between the health regions and different communities as well.

We used direct standardization to calculate age-adjusted and sex-specific CKD distributions among four health regions. Age-adjustment, also known as age standardization, is used to compare populations with variable age groups. To determine the age-adjusted rate, we first calculate the age-specific CKD rates for each age group by dividing the respective population CKD number, and multiply by 1,000.[123] Direct age-standardized and sex specific prevalence were calculated using Statistics Canada's Canadian Socio-Economic Information Management System (CANSIM) table 109-5355.

Kidney function stability was measured by the progression of CKD, a rate of kidney function decline per year. If kidney function drops at a rate of equal to or greater

than 5 ml/min/1.73m^2 (measured by eGFR$_{MDRD}$) per year, this is considered unstable or progressive chronic kidney disease.90

We used a **logistic regression** model to evaluate the likelihood of an individual being seen by a nephrologist by patients' demographics (age, sex, diabetes status, CKD stage and stability of kidney function).

Logistic regression was applied since the dependent variable is dichotomous (either being seen by a nephrologist or not). The Odds ratio and 95% CI were calculated to assess the association of nephrologist visits by patients' characteristics. A P value less than 0.05 was considered to indicate statistical significance.

On clinical grounds, all of the following parameters are relevant potential predictors, and thus we decided to enter them all into the model at the same time. We did not perform stepwise addition or deletion. In developing a logistic model, we first decided which variables of the data to which we had access will be clinically relevant, and then, we used the enter method to force them all into the model at the same time to allow for multivariable adjustment. Omnibus test was used to compare the fitted model against the intercept-only model.

The null hypothesis for the overall model fit: The overall model does not predict nephrologist visit; the independent variables as a group are not related to being seen by a nephrologist.

The alternative hypothesis for the overall model fit: The overall model predicts the likelihood of a nephrologist visit. Being younger (vs. older), male (vs. female), having diabetes (vs. not diabetic), living in different health regions, having unstable kidney function, and low average eGFR per year are related to the likelihood of being seen by a nephrologist.

Using **generalized linear models (GLMs)**, we assessed the association between the frequency of nephrology visits during the study period (the dependent variable), and independent variables (age, sex, diabetes status, eGFR, health region and kidney function stability). Unlike linear models in which the distribution of the dependent variable needs to be normally distributed, GLMs allow the dependent variable to be any member of an exponential family (e.g. binomial, Poisson, multinomial etc.).[124] In this study, the dependent variable is the frequency of nephrologist visits, which is a count variable and also shows skewed distribution; hence, the Poisson regression analysis, under GLMs, was used. The GLM analysis was, thus, limited to those CKD patients who had at least one nephrology visit. Individuals without nephrologist visits were not included in this analysis. Adjusted odds ratios are presented to illustrate the association of nephrologist visit frequencies with independent variables. Comparisons between categories such as CKD stages were considered statistically significant with a p-value less than 0.05. Omnibus test for Poisson regression was used to compare the fitted model against the intercept-only model.

Missing information is only the values where the specific missing piece of data is needed to perform a particular analysis. For example, if postal code is missing for a patient with CKD, that person is not included in the geographic distribution analysis but is included in other analyses, such as the analysis of the frequency of nephrologist visits.

The Statistical Package of Social Science (IBM SPSS Statistics for Windows, Version 22, Armonk, NY: IBM Corp.) was used to perform all statistical analyses.

2.10   Ethical considerations

2.10.1 Protection of Human Research Participants (PHRP)

As the study involved the analysis of de-identified past records and did not have any direct contact with Human Research Participants (HRP), there were no physical or medical risks involved. The study protocol approval from the Provincial ethics review board was obtained (Researcher Portal File #: 20170288; study 2016.153) and the study was conducted in conformity with the Tri-Council Policy Statement (TCPS 2).

2.10.2 Data safety, security, and confidentiality

All due precautions as prescribed in the TCPS 2 were taken to safeguard the confidentiality of the information derived from the NLCHI data set. Each complete data file included only a study code unique identifier (Study ID) ensuring that any patient identifier was removed by NLCHI staff before the data was made available for analysis.

The data regarding linkages between the study data set and the original data set was kept in the custody of NLCHI. The data was linked first and then de-identified by NLCHI, who then sent it to the Center for Health Informatics and Analytics (CHIA) at MUN.

2.10.3 Data retention and disposal after the retention period

Any hard copies of data were kept in a locked cabinet at CHIA with Mitch Sturge (Associate Director, CHIA room # 4M419; 709.864.6440; mitch.sturge@med.mun.ca)

Once the project was completed, research data was secured and will be kept for 5 years. At the end of the data retention period, all data will be securely removed by a thorough data removal procedure according to the MUN data retention and disposal policy. Stored data will be erased by using multiple passes of data wiping software to ensure that the data will not be retrievable using recovery methods.

2.11 Funding sources

This project was funded by a Translational and Personalized Medicine Initiative (TPMI)/NL SUPPORT Educational grant. All funding was administered through the Office of Research & Graduate Studies, the Faculty of Medicine and University Finance Office.

Chapter 3: Results

Considering the 438 communities that the CKD patients reside in, a total of all 40,465 patients were taken into account in this study. Of them, 188 communities were from the Eastern RIHA followed by 135, 69, and 46 communities from the Central RIHA, Western RIHA and Labrador-Grenfell RIHA, respectively. The distribution of these communities is shown in the map (Figure 3 and 4). Among these communities, the larger communities were St. John's (CKD, N=9,457), Carbonear (657), Burin (198), Clarenville (1,070) and Bonavista (670) from the ERIHA (29,457); Gander (355) and Grand-Falls-Windsor (483) from the CRIHA (3,354); Corner Brook (2,126), Stephenville (500), and Port-aux-Basques (509) from the WRIHA (6,237); and St. Anthony (181), Happy Valley-Goose Bay (140), and Labrador City (79) from the Labrador-Grenfell (1,239) Health authority.

Figure 3: Distribution of CKD communities in Newfoundland and Labrador.

Figure 4: Number of CKD cases across communities in Newfoundland and Labrador.

3.1 Baseline characteristics

The numbers of identified CKD people within each of the variables of interest are presented in Table 1.

Table 1: Baseline characteristics of the study population

Variables	Number of CKD patients (%)
The number of people in the cohort	40465
Age (years)	
18-39	561 (1.4%)
40-49	1,970 (4.9%)
50-59	5,918 (14.6%)
60-69	12,048 (29.8%)
70+	19,865 (49.1%)
Missing	103 (0.2%)
Male	15,948 (39.4%)
Diabetes	16,663 (41.2%)
RIHA	
ERIHA	29,457 (72.8%)
CRIHA	3,354 (8.3%)
WRIHA	6,237 (15.4%)
G-Labrador	1,239 (3.1%)
Missing	178 (0.4%)
Nephrologist Visit	8,550 (21.2%)

*103 CKD individuals had no information about their age; 178 CKD did not have postal code information; eGFR= Estimated glomerular filtration rate; RIHA=Regional Integrated Health Authority; ERIHA=Eastern RIHA; CRIHA=Central RIHA; WRIHA=Western RIHA; G-Labrador=Labrador-Grenfell RIHA

3.2   Distribution of CKD by age across RIHA communities, 2011-15

When considering all years of the study, the proportion of CKD patients at different age groups varied widely across regions. In most communities, the highest CKD proportion were in the older age group, except in Labrador City, where the highest proportion was seen within the middle-aged population (36.7% in age 60-69 and 26.6% in age 50-59 vs. 24.1% in age 70+). Also, table 2 suggests that those aged 40-49 years in Labrador city were more likely to have CKD (10.1%) compared to those of the same age group in other communities (Table 2).

Table 2: Distribution of CKD across RIHA communities by age (2011-15)

Year	Age Group (years)	NL (N=528,448)	Eastern RIHA					Central RIHA		Western RIHA			Labrador-Grenfell RIHA		
			St. John's (N=108,860)	Carbonear (N=4,838)	Burin (N=2,424)	Clarenville (N=6,291)	Bonavista (N=3,448)	Gander (N=11,688)	Grand-Falls-Windsor (N=14,171)	Corner Brook (N=19,806)	Stephenville (N=6,719)	Channel-Port-aux-Basques (N=4,170)	St. Anthony (N=2,418)	Happy Valley-Goose Bay (N=8,109)	Labrador City (N=9,354)
2011-15	18-39	1.4	1.4	1.4	1.5	2.2	1.0	2.3	1.7	1.0	0.4	1.2	0.6	1.4	1.3
	40-49	4.9	4.7	3.8	5.1	5.8	5.2	4.8	2.1	2.4	3.2	3.1	6.1	7.9	10.1
	50-59	14.6	13.1	12.2	16.2	14.4	15.4	10.1	9.7	11.1	13.6	10.2	11.0	15.7	26.6
	60-69	29.8	26.1	28.5	37.9	26.2	26.1	21.1	26.9	27.1	26.6	30.3	32.6	30.7	36.7
	70+	49.1	54.5	54.0	39.4	51.2	51.8	61.4	59.2	58.0	55.8	55.0	49.7	43.6	24.1

*N=number of population (as denominator); RIHA=Regional Integrated Health Authority; numbers are presented as %; census 2011

3.3   Distribution of CKD by RIHA communities by stage

The proportions of CKD population, within each CKD stage, showed a fairly

consistent rise for the first four years and then fall in last year of the study period. This is

possibly due to the method used to identify CKD which requires two measurements

below a cutoff at least three months apart. Some people who truly have CKD would

have a single final creatinine in 2011 while others would have a single first creatinine in

2015. Both were excluded from the original data due to their not meeting the case

definition. This would artefactually affect the prevalence and the pattern we see. For

this reason, we chose the year 2013 to comment on comparisons across communities.

Among CKD patients in 2013, Bonavista (11.75%) showed the highest prevalence

of mild to moderate kidney dysfunction (eGFR$_{MDRD}$: 45-59 ml/min/1.73m^2), followed by

Clarenville (10.67%) and Carbonear (9.45%) from the ERIHA. Channel Port-Aux-Basque

from the WRIHA exhibited a 7.65% prevalence rate of mild to moderate kidney

dysfunction while St. Anthony from LGRIHA showed a rate of 5.00% in 2013. Prevalence

rates of moderate to severe CKD (<45 ml/min/1.73m^2), severe CKD (<30), and end stage

kidney disease (<15), were highest in Bonavista (5.16%, 1.39%, and 0.09%, respectively)

(Table 3).

Table 3: Distribution of CKD RIHA communities by level of eGFR (2011-15)

	RIHA		Eastern					Central		Western			Labrador-Grenfell		
	Community	NL (N=528,448)	St. John's (N=108,860)	Carbonear (N=4,838)	Burin (N=2,424)	Clarenville (N=6,291)	Bonavista (N=3,448)	Gander (N=11,688)	Grand-Falls-Windsor (N=14,171)	Corner Brook (N=19,806)	Stephenville (N=6,719)	Channel-Port-aux-Basques (N=4,170)	St. Anthony (N=2,418)	Happy Valley-Goose Bay (N=8,109)	Labrador City (N=9,354)
eGFR <60	2011	3.44	3.89	6.06	3.34	7.36	8.58	1.31	1.44	6.24	3.91	6.71	4.05	0.69	0.32
	2012	4.04	4.63	7.73	4.08	8.08	9.45	1.69	1.83	6.30	4.44	6.71	4.51	0.86	0.41
	2013	4.89	5.65	9.45	4.91	10.67	11.75	1.75	1.81	7.50	5.39	7.65	5.00	1.09	0.50
	2014	5.18	5.73	9.98	5.49	11.64	12.53	1.36	1.91	7.96	5.58	9.26	6.29	1.46	0.65
	2015	4.30	4.60	9.82	5.24	9.90	11.54	1.45	1.83	4.58	2.99	4.96	6.37	1.21	0.56
eGFR <45	2011	1.21	1.31	2.36	1.36	2.34	3.48	0.53	0.75	2.14	1.46	2.54	1.74	0.21	0.13
	2012	1.41	1.54	3.16	1.94	2.64	4.15	0.69	0.92	2.12	1.70	2.49	1.82	0.33	0.14
	2013	1.68	1.84	3.53	1.94	3.13	5.16	0.78	0.99	2.75	2.08	3.21	2.23	0.41	0.20
	2014	1.78	1.85	3.66	1.98	3.48	5.10	0.62	0.98	2.91	2.23	3.41	2.52	0.53	0.27
	2015	1.54	1.50	3.78	1.77	3.12	4.50	0.67	0.95	1.96	1.41	2.09	2.73	0.49	0.20
eGFR <30	2011	0.27	0.26	0.39	0.37	0.70	0.75	0.15	0.26	0.41	0.39	0.50	0.33	0.00	0.02
	2012	0.33	0.34	0.62	0.45	0.79	0.90	0.21	0.33	0.40	0.37	0.72	0.45	0.02	0.04
	2013	0.40	0.41	0.74	0.41	0.75	1.39	0.24	0.28	0.60	0.48	0.89	0.41	0.07	0.02
	2014	0.43	0.40	0.97	0.50	0.78	1.42	0.21	0.30	0.64	0.45	0.96	0.70	0.09	0.05
	2015	0.39	0.34	0.93	0.50	0.75	1.39	0.25	0.34	0.47	0.33	0.53	0.91	0.11	0.05
eGFR <15	2011	0.01	0.01	0.00	0.00	0.02	0.00	0.01	0.04	0.01	0.03	0.00	0.00	0.00	0.00
	2012	0.02	0.02	0.00	0.00	0.03	0.03	0.01	0.03	0.03	0.01	0.02	0.00	0.00	0.00
	2013	0.03	0.03	0.02	0.00	0.06	0.09	0.02	0.04	0.03	0.03	0.02	0.00	0.00	0.00
	2014	0.04	0.03	0.04	0.00	0.05	0.12	0.02	0.04	0.05	0.06	0.02	0.04	0.00	0.00
	2015	0.04	0.04	0.06	0.08	0.10	0.20	0.01	0.04	0.06	0.01	0.02	0.17	0.00	0.02

*N=number of population (as denominator); RIHA=Regional Integrated Health Authority; eGFR=estimated glomerular filtration rate (ml/min/1.73m^2); all numbers are presented as %.

3.4   Distribution of CKD in NL by stage in relation to age, sex, and diabetes status

In NL, moderate to severely decreased kidney function (eGFR <45, <30 and <15 ml/min/1.73m^2) patients were mostly in the older (70+ years) age group, more likely to be female, and more likely to have diabetes. However, the majority (54.6%, 57.6%, and 57.9%) of mild to moderate CKD (eGFR <60 ml/min/1.73m^2) patients were below 70 years of age and did not have diabetes mellitus during 2013, 2014, and 2015 respectively (Table 4).

The proportion of 70+ years individuals with CKD dropped in each stage over every year considered by the study. The proportions of those with CKD under 70 years of age tended to remain stable or increase in each stage over the study's time-period.

Table 4: Distribution of CKD by level of eGFR, time (2011-15), age, sex and diabetes status

		Age Groups (years)					Gender		Diabetes status	
	Year	18-39	40-49	50-59	60-69	70+	Male	Female	Yes	No
*eGFR <60	2011	0.7	3.6	12.4	29.8	53.2	39.3	60.7	42.6	57.4
	2012	0.9	3.5	13.3	30.8	51.2	39.1	60.9	40.4	59.6
	2013	1.1	4.6	15.3	33.3	45.4	39.2	60.8	37.6	62.4
	2014	1.2	5.1	16.6	34.4	42.4	39.3	60.7	36.1	63.9
	2015	1.1	5.2	16.6	34.8	42.1	39.1	60.9	37.3	62.7
eGFR <45	2011	0.5	1.7	6.4	19.8	71.4	37.7	62.3	52.9	47.1
	2012	0.6	2.0	6.5	19.9	70.8	37.1	62.9	51.3	48.7
	2013	0.6	2.1	7.2	21.8	68.0	37.1	62.9	50.8	49.2
	2014	0.7	2.3	8.0	24.1	64.6	37.1	62.9	51.1	48.9
	2015	0.7	2.4	8.6	25.4	62.6	38.9	61.1	50.9	49.1
eGFR <30	2011	1.0	1.6	6.0	12.7	78.6	35.4	64.6	57.9	42.1
	2012	0.6	1.8	5.8	14.5	77.0	37.0	63.0	57.8	42.2
	2013	0.8	2.1	5.7	15.4	75.7	36.0	64.0	57.3	42.7
	2014	0.8	2.3	7.3	17.4	71.9	37.0	63.0	57.8	42.2
	2015	0.8	2.8	7.7	19.4	69.0	38.5	61.5	58.9	41.1
eGFR <15	2011	0.00	2.90	2.90	13.04	81.16	30.43	69.57	55.07	44.93
	2012	0.00	3.74	8.41	14.02	73.83	23.36	76.64	57.01	42.99
	2013	0.72	2.17	10.14	13.77	73.19	34.78	65.22	62.32	37.68
	2014	1.54	4.62	9.23	16.92	67.18	31.28	68.72	57.44	42.56
	2015	3.03	4.76	9.96	21.65	60.17	36.80	63.20	60.17	39.83

*eGFR=estimated glomerular filtration rate measured in ml/min/1.73m^2; all numbers are presented as %; Number of populations in NL=528,448 (as denominator)

3.5 Frequency of eGFR measurements

Similarities were noted in the average frequency of kidney function tests (eGFR) for CKD patients among communities over the study period, but the averages were not identical (Table 5 and 6). In 2011, the range of average eGFR test frequency was between 3 and 5 tests per year. Test counts jumped to 9 tests per year in some communities (Carbonear, 9.6±0.7 and St. Anthony, 9.3±0.8) in 2015.

For communities in the Eastern Health Region, eGFR test-counts have hovered in the range of 7-9 tests per year for the past few years. However, eGFR test counts have decreased in some Western Health Region communities (for example, in Corner Brook, the average test-counts were 7.5±0.2 in 2014 and 3.5±0.1 in 2015).

Communities from the Central Health Region showed a steady eGFR test-count of 3.4 to 4.1 tests per year for five consecutive years from 2011 to 2015. eGFR test count for coastal Indigenous communities increased in last two years (7.9±0.7 in 2014 and 7.0±0.8 in 2015) compared to the previous years (3.4±0.4 in 2011, 4.9±0.5 in 2012, and 4.4±0.3 in 2013).

Variations in eGFR test frequencies between age groups can be seen in Table 6. Two age groups (young adult, 18-39 years, and elderly, 70+ years) have a higher frequency of eGFR tests compared to the middle age groups. An even greater variation was observed between diabetic and non-diabetic CKD patients across the province (such

as, 8.3±3.7 eGFR tests for diabetic patients in 2013, compared to 6.1±2.7 eGFR tests for

non-diabetic patients). The frequency of eGFR tests for female CKD patients was slightly

lower throughout the study period than for male patients (i.e., in 2013, the eGFR test-

count frequency was 7.3±4.7 for males vs 6.8±4.4 for females).

Table 5: Frequency of CKD eGFR testing across RIHAs and communities (2011-15)

	eGFR test frequency (Mean+SE) each year				
	2011	2012	2013	2014	2015
Overall, NL (N=40465)	4.7±0.0	6.2±0.0	7±0.1	7.4±0.1	6.9±0.1
ERIHA (N=29457)	5±0.1	6.5±0.1	7.4±0.1	7.8±0.1	7.5±0.1
CRIHA (N=3354)	3.4±0.1	4.1±0.1	4.1±0.1	3.9±0.1	3.4±0.1
WRIHA (N=6237)	4.5±0.1	5.9±0.1	6.8±0.1	7.1±0.1	3.5±0.1
G-Labrador (N=1239)	3.1±0.2	4.2±0.2	4.9±0.2	6.8±0.3	7.7±0.3
ERIHA (N=29457):					
St. John's (N=9457)	5.3±0.1	7.0±0.1	7.7±0.1	7.7±0.1	7.5±0.1
Carbonear (N=657)	4.1±0.3	5.5±0.5	6.8±0.4	8.3±0.4	9.6±0.7
Burin (N=198)	5.9±0.5	6.8±0.6	8.6±0.8	9.6±1.0	8.9±0.6
Clarenville (N=1070)	4.5±0.2	5.8±0.2	6.6±0.2	7.8±0.3	7.1±0.2
Bonavista (N=670)	5.7±0.2	7.2±0.4	8.3±0.4	9.2±0.4	7.9±0.3
CRIHA (N=3354):					
Gander (N=355)	3.2±0.2	3.9±0.3	3.8±0.3	3.6±0.3	3.5±0.4
Grand Falls Windsor (N=483)	3.3±0.2	3.9±0.2	3.9±0.2	3.8±0.4	3.5±0.2
WRIHA (N=6237):					
Corner Brook (N=2126)	4.7±0.1	6.1±0.2	7.1±0.2	7.5±0.2	3.5±0.1
Stephenville (N=500)	4.5±0.2	5.7±0.4	6.2±0.4	6.3±0.3	3.3±0.2
Channel Port Aux Basques (N=509)	4.1±0.2	5.3±0.3	6.8±0.4	6.8±0.3	3.7±0.2
G-Labrador (N=1239):					
St. Anthony (N=181)	2.6±0.2	4.4±0.7	5.7±0.9	7.2±0.7	9.3±0.8
Happy Valley-Goose Bay (N=140)	3.6±0.4	5.1±0.5	6.2±0.8	8.9±0.9	5.6±0.7
Labrador City (N=79)	3.8±0.5	4.9±0.6	5.4±0.6	7.7±1.2	4.9±0.7
Indigenous Coastal communities (N=133)	3.4±0.4	4.9±0.5	4.4±0.3	7.9±0.7	7.0±0.8

*eGFR=estimated glomerular filtration rate measured in ml/min/1.73m2; SE=standard error; N=number of CKD (as denominator); RIHA=Regional Integrated Health Authority; ERIHA=Eastern RIHA; CRIHA=Central RIHA; WRIHA=Western RIHA; G-Labrador=Labrador-Grenfell RIHA

Table 6: Frequency of CKD eGFR testing in NL by Age, sex and diabetes status (2011-15)

NL (N=40465)	eGFR test frequency (Mean+SE) each year				
	2011	2012	2013	2014	2015
Age (years), 18-39	4.6±3.3	5.7±4.4	7.5±5.2	8.3±3.9	7.4±3.1
40-49	4.1±3.9	5.7±5.8	6.7±5.9	6.1±2.9	6.3±2.8
50-59	4.3±4.2	5.5±5.4	6.4±4.4	6.9±3.1	6.5±2.6
60-69	4.3±3.9	5.6±4.9	6.7±4.5	7.1±3.2	6.6±2.5
70+	5.2±4.3	6.7±5.5	7.4±4.3	7.8±3.3	7.2±2.3
Sex, Male	4.9±4.3	6.5±5.6	7.3±4.7	7.8±3.4	7.3±2.6
Female	4.6±4.1	5.9±5.1	6.8±4.4	7.1±3.1	6.6±2.4
Diabetes status, Yes	5.5±3.2	7.4±4.3	8.3±3.7	8.8±2.8	8.2±1.9
No	4.1±2.4	5.3±3.1	6.1±2.7	6.4±2.0	5.9±1.4

*eGFR=estimated glomerular filtration rate measured in ml/min/1.73m2; SE=standard error; N=number of CKD (as denominator); RIHA=Regional Integrated Health Authority; ERIHA=Eastern RIHA; CRIHA=Central RIHA; WRIHA=Western RIHA; G-Labrador=Labrador-Grenfell RIHA

3.6   Nephrology visits across patients' demographics and clinical characteristics

Eight thousand, eight hundred fifty CKD patients who had seen a nephrologist, and 31,615 patients who were not seen by a nephrologist at any time during the 5-year study period (2011-2015), were taken into consideration for comparison purposes. (Table 7) The mean age of CKD patients without nephrologist visits was 68.9±12.0 years, compared to the mean age of those who had at least one nephrologist visit, which was 68.3±12.5 years. The highest proportion of younger CKD patients who were seen by a nephrologist was exhibited in WRIHA (59.6%), compared to the ERIHA, CRHIA and Labrador-Grenfell health regions (28.5%, 35.1%, and 50.0%, respectively). Overall, in Newfoundland, only 32.3% of CKD patients aged 18-39 years saw a nephrologist. In WRIHA, CKD patients are more likely to see a nephrologist, but a lot of people are still not being seen. In NL, 21.5% of 70+ age CKD patients are actually seen, while 46.4% are seen in WRIHA. Nephrologists in WRIHA are seeing almost half of the people over 70 years old with CKD. This is a high proportion compared to anywhere else.

Among males with identifiable CKD, 46.9% were seen by a nephrologist in WRIHA, compared to 19%, 22.5%, and 30.3% in ERIHA, CRIHA, and Labrador-Grenfell health regions, respectively. Interestingly, the proportions of male CKD patients seen by a nephrologist are higher than the proportion of female CKD patients seen by a nephrologist in all four health regions.

As expected the diabetic patients with CKD are more likely to be seen by a nephrologist compared to non-diabetic patients with CKD. Again, the highest proportion of diabetic patients with CKD who were seen by a nephrologist was seen in WRIHA (48%), compared to the other health regions (21.5%, 22.4%, and 28.1% in ERIHA, CRIHA, and Labrador-Grenfell, respectively).

In general, when we look according to the eGFR levels, the bulk of those who have really bad kidney function get seen by a nephrologist, but very few people with more preserved kidney function get seen. Specifically, in WRIHA and Labrador-Grenfell, all identifiable CKD patients who are at stage 5 were seen by a nephrologist compared to those in ERIHA (80.6%) and CRIHA (71%). Only about 9% of stage 3a CKD patients from CRIHA were referred to a nephrologist. This proportion is slightly higher in ERIHA (12.2%) and Labrador-Grenfell (13.2%), whereas WRIHA showed the highest referral rates for CKD patients in that eGFR stage.

Table 7: Comparison of variables specific proportion of CKD population who were seen by a nephrologist:

	Proportion of CKD population seen by a nephrologist by given characteristics				
	NL	ERIHA	CRIHA	WRIHA	G-Labrador
Age, 18-39	32.3	28.5	35.1	59.6	50.0
40-49	25.1	21.1	38.4	48.1	27.4
50-59	19.9	16.3	23.7	37.3	24.6
60-69	19.9	15.9	19.2	39.1	25.0
70+	21.5	16.2	16.8	46.4	19.6
Sex, Male	24.0	19.0	22.5	46.9	30.3
Female	19.3	15.1	16.5	40.8	17.9
Diabetes status, Yes	26.4	21.5	22.4	48.0	28.1
No	17.4	13.4	15.7	39.3	18.1
eGFR <60	16.0	12.2	8.9	36.7	13.2
<45	35.3	31.0	27.8	56.7	40.0
<30	62.5	60.4	50.3	80.9	78.1
<15	80.4	80.6	71.0	100.0	100.0
Stable kidney	21.0	16.4	19.4	42.8	22.7
Unstable kidney	25.0	22.2	15.5	60.3	20.9

*all numbers are presented as %; eGFR=estimated glomerular filtration rate measured in ml/min/1.73m^2; NL=Newfoundland and Labrador; RIHA=Regional Integrated Health Authority; ERIHA=Eastern RIHA; CRIHA=Central RIHA; WRIHA=Western RIHA; G-Labrador=Labrador-Grenfell RIHA

3.7   Association between nephrologist visit and patients' demographics and clinical characteristics

The logistic regression analysis showed strong evidence of a difference between health regions and referral to nephrologist. (Table 8) Adjusted odds for nephrologist visit were 3.4 folds (95% CI, 2.9-3.9) for WRIHA, 0.5 (95% CI, 0.4-0.6) for CRIHA, and 0.8 (95% CI, 0.7-0.9) for ERIHA respectively compared to Labrador-Grenfell RIHA. Male CKD patients have a 1.4-fold (OR, 1.4; 95% CI, 1.3-1.5) (p < 0.001) higher chance of seeing a nephrologist than female individuals. The presence of diabetes demonstrated an association with a higher likelihood of a nephrologist visit (odds ratio: 1.4 CI, 1.3-1.5) (p < 0.001). CKD patients with unstable kidney function have a significantly higher chance of seeing a nephrologist than stable CKD patients (odds ratio: 2.2 CI, 1.9-2.4) (p < 0.001).

The interaction term between Age and average eGFR is significant but does not show any higher or lower chance of seeing a nephrologist. The main effects of lower eGFR (OR, 0.8; 95% CI, 0.8-0.9) (p < 0.001) and younger age (OR, 0.9; 95% CI, 0.92-0.93) (p<0.001) may be associated with a greater likelihood of being seen by a nephrologist.

Omnibus test of model coefficients based on the likelihood-ratio chi-square test showed that the overall model (with independent variables included) is predictive of nephrologist visit. Highly significant chi-square (6738.5, df=9, p< .001) suggests that the overall model of expecting a nephrologist visit is significantly better and more suitable compared to intercept-only base model.

Table 8: Multivariate logistic regression analysis for predictors of referral to nephrologists.

| | Variables in the Equation | | | | | | | |
| | B | SE | Wald | df | Significance (p value) | OR | 95% CI for OR | |
							Lower	Upper
Age (at baseline)	-.074	.005	235.351	1	.000	.929	.920	.937
Sex (Male)	.352	.027	164.407	1	.000	1.422	1.347	1.500
Diabetes status (Yes)	.368	.027	178.934	1	.000	1.444	1.369	1.524
ERIHA	-.186	.075	6.125	1	.013	.830	.716	.962
CRIHA	-.581	.088	43.600	1	.000	.559	.471	.665
WRIHA	1.224	.079	242.722	1	.000	3.402	2.916	3.968
G-Labrador			2062.413	3	.000			
Kidney Function Stability (Unstable)	.779	.067	135.329	1	.000	2.178	1.911	2.484
Avg eGFR	-.129	.007	365.836	1	.000	.879	.867	.890
Age*Avg eGFR	.001	.000	67.863	1	.000	1.001	1.001	1.001
Constant	7.244	.364	395.068	1	.000	1399.17		

* The outcome in the regression was whether a person see a nephrologist or not?
Variable(s) entered in the final model: Age (at baseline), Sex, Diabetes status, RIHA, Kidney Function Stability, Avg eGFR, Age*Avg eGFR; eGFR=estimated glomerular filtration rate measured in ml/min/1.73m^2; B=Beta coefficient; SE=standard error; df=Degree of freedom; OR=odd ratio; CI=Confidence interval; Avg eGFR= Average eGFR; RIHA=Regional Integrated Health Authority; ERIHA=Eastern RIHA; CRIHA=Central RIHA; WRIHA=Western RIHA; G-Labrador=Labrador-Grenfell RIHA

3.8   Kidney care delivery

Overall, 7.36% of CKD patients were in contact with nephrologists, irrespective of age, sex and level of kidney dysfunction within one year of CKD recognized. The rate was 10.81% within two years after recognition. The proportion of nephrologist visits were 16.03% and 24.27% in the first and second year, respectively, for CKD patients in the Western Health Region. The Eastern, Central and Labrador-Grenfell Health Regions were 5.76% and 8.17%, 5.40% and 8.88%, 7.02% and 10.82%, respectively. Among CKD patients within the Western Health authority, Corner Brook had the highest rate of nephrologist visits within one and two years after CKD recognition (21.07% and 30.53%, respectively). If a CKD patient is living in St. John's, he or she is about 6.6% and 9.5% likely to see a nephrologist within the first and second year, respectively, after CKD recognition. If a patient is living in Corner Brook, he or she is much more likely to see a nephrologist (Table 9).

As expected, the age-specific rates of young CKD patients, aged 18-39, had the highest nephrologist visits among all age groups within both one and two years after recognition. Rates also increased in patients with diabetes compared to patients without diabetes. Female individuals were less likely to have nephrologist visits than male individuals (6.7% vs 8.4% in the first year and 9.9 vs. 12.2% in the 2nd year, after CKD recognition) (Table 10).

Table 9: Distribution of CKD by nephrologist visit within one and two years following recognition by RIHAs and communities

	Nephrologist visit within 1yr after recognition	Nephrologist visit within 2yrs after recognition
Overall, NL (N=40465)	7.36	10.81
ERIHA (N=29457)	5.76	8.17
CRIHA (N=3354)	5.40	8.88
WRIHA (N=6237)	16.03	24.27
G-Labrador (N=1239)	7.02	10.82
Communities		
ERIHA (N=29457):		
St. John's (N=9457)	6.59	9.49
Carbonear (N=657)	3.35	4.87
Burin (N=198)	5.56	6.57
Clarenville (N=1070)	2.90	4.02
Bonavista (N=670)	4.03	6.12
CRIHA (N=3354):		
Gander (N=355)	3.38	7.32
Grand Falls Windsor (N=483)	4.55	8.49
WRIHA (N=6237):		
Corner Brook (N=2126)	21.07	30.53
Stephenville (N=500)	9.40	15.00
Channel Port Aux Basques (N=509)	11.79	19.25
G-Labrador (N=1239):		
St. Anthony (N=181)	6.63	10.50
Happy Valley-Goose Bay (N=140)	8.57	10.13
Labrador City (N=79)	6.33	10.13

*N=number of CKD (as denominator); numbers are presented as %;
NL=Newfoundland and Labrador; RIHA=Regional Integrated Health Authority;
ERIHA=Eastern RIHA; CRIHA=Central RIHA; WRIHA=Western RIHA;
G-Labrador=Labrador-Grenfell RIHA

Table 10: Distribution of CKD in NL by nephrologist visit within one and two years following recognition by age, sex and diabetes status

	Nephrologist visit within 1yr after recognition	Nephrologist visit within 2yrs after recognition
Age groups, 18-39 (N=561)	11.9	18.2
40-49 (N=1,970)	8.3	12.1
50-59 (N=5,918)	6.9	10.2
60-69 (N=12,048)	6.7	10.0
70+ (N=19,865)	7.7	11.2
Gender, Male (N=15,948)	8.4	12.2
Female (N=24,516)	6.7	9.9
Diabetes status, Yes (N=16,663)	9.0	13.3
No (N=23,802)	6.2	9.0

*N=number of CKD (as denominator); all numbers are presented as %;
RIHA=Regional Integrated Health Authority; NL=Newfoundland and Labrador

3.9   Direct age-standardized rate for nephrologist visits

CKD patients seeing nephrologists from the Eastern Health region experienced rates similar to the provincial rates (7-9 per 1,000). The communities with the highest number of male and female CKD patients seeing nephrologists were found in the Western Health Region (around 17 per 1000) throughout the study period. As expected, the rates in Central and Labrador-Grenfell were much lower (2-5 per 1000), compared to the NL average (Figure 5).

Also, when compared to the age-standardized number of visits to a nephrologist by CKD patients per 1,000, the Western Health Region population (both male and female) showed higher rates than the other three health regions (for example, in 2013, visit rates to a nephrologists were 30.80 per 1,000 in the Western Health Region compared to 16.97, 8.24, and 6.53 in the Eastern, Central and Labrador-Grenfell Health Regions, respectively) (Figure 6).
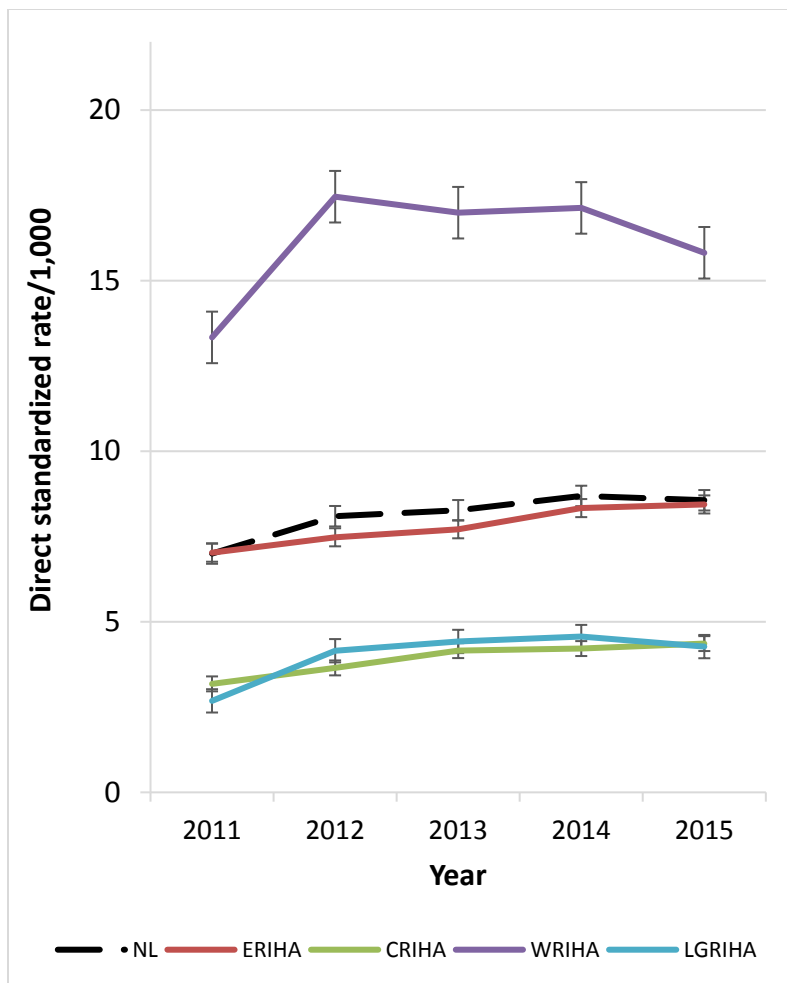
(A) Male
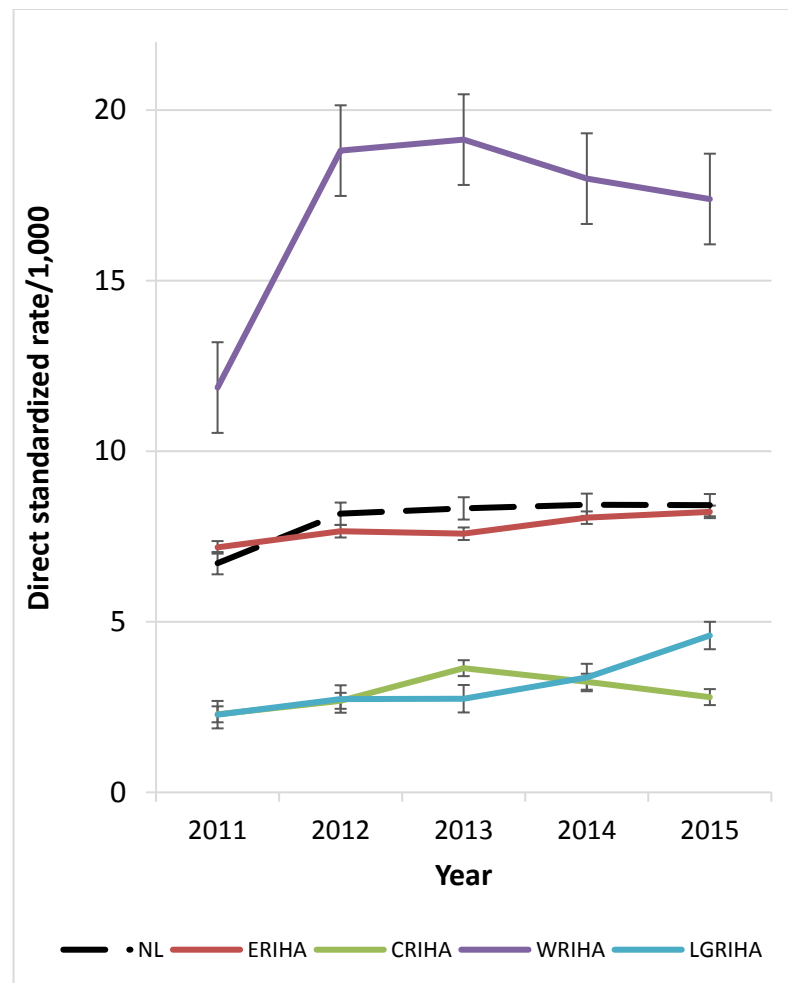
(B) Female

Figure 5: Age-adjusted nephrologist visit by sex across health regions.
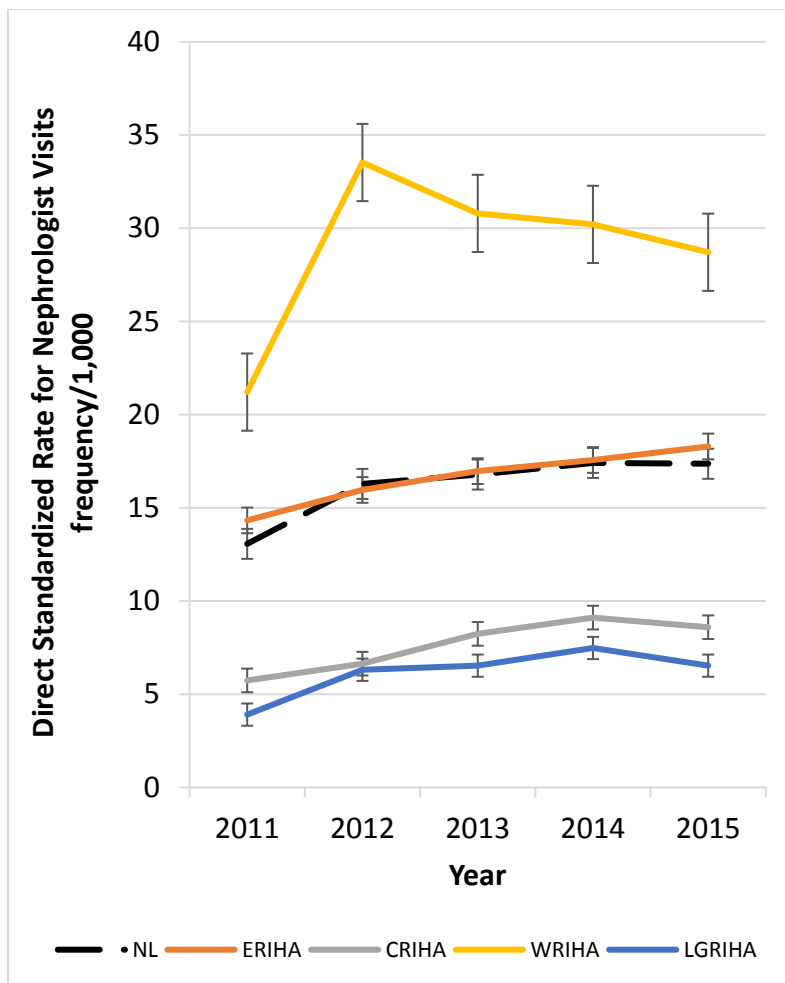
(A) Male
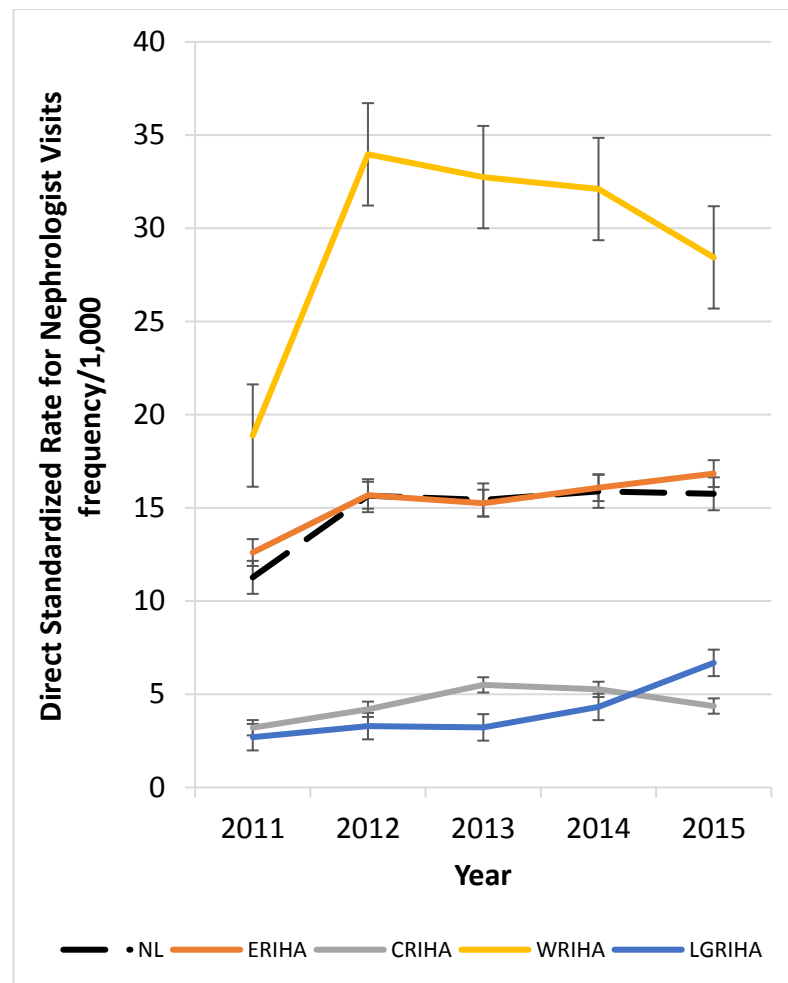
(B) Female

Figure 6: Frequency of age-adjusted nephrologist visit by sex across health regions.

3.10   Factors influencing the frequency of nephrologist follow-ups

The odds ratios of nephrologist visits were 1.5 (CI: 1.4-1.6, p<.0001), 1.4 (CI: 1.3-1.4, p<.0001), 1.4 (CI: 1.3-1.44, p<.0001), and 1.2 (CI: 1.1-1.2, p<.0001) times higher for the young adult (18-39 years), 40-49, 50-59, and 60-69 age groups, respectively, compared to the age group of 70 years and over. Nephrologist visit frequency decreased as average age increased. (Table 11)

Female CKD patients had a lower likelihood of seeing a nephrologist in comparison to their male counterparts (OR=1.2, 95% CI: 1.2-1.3, p<.0001), as determined after adjusting all independent variables in the Poisson regression model. Follow up frequency was slightly higher for diabetic CKD patients than for those who had CKD with no diabetes mellitus (OR=1.1, 95% CI: 1.0-1.1, p<.0001).

The frequency of nephrologist visits varied by the level of kidney dysfunction. Using the average eGFR values over the study period from 2011-2015, low eGFR patients (stage 5 CKD, <15ml/min/1.73m^2) showed higher odds (OR=4.0, 95% CI: 3.8-4.3, p<.0001) than people with an eGFR over 60 ml/min/1.73m^2 after adjusting all other variables in the model. The next most frequent nephrologist visits were observed among patients with stage 4 CKD (OR=2.3, 95% CI: 2.2-2.4, p<.0001) followed by stage 3b CKD (OR=1.3, 95% CI: 1.3-1.4, p<.0001).

Regional differences were also observed. The Eastern, Western and Central integrated health regions were associated with the likelihood of higher frequency of nephrologist visits compared to Labrador-Grenfell (OR=1.8, 95% CI: 1.7-2.0, p<.0001;

OR=1.7, 95% CI: 1.6-1.8, p<.0001; and OR=1.3, 95% CI: 1.2-1.4, p<.0001,

respectively).

Chronic kidney disease patients with unstable kidney dysfunction (patients with

a rate of kidney function decline of more than 10ml/min/1.73m2 eGFR$_{MDRD}$ per year

on average) were found to have an odd pattern of care. There was 10% lower

chance of having frequent nephrologist-visits (OR=0.9, CI: 0.8-0.9, p<.0001) for

unstable kidney function patients than those with stable kidney dysfunction. It is

possible that nephrologists may ignore previous follow ups and overlook the change

of kidney function; rather they look at the current or most recent kidney function

test reports.

Omnibus test showed statistically significant fitted model (LR chi-square 5576.3,

df=14, p<.001) against the intercept-only model. A diabetic younger male with low-

average eGFR per year and unstable kidney function were seen more frequently by a

nephrologist. CKD patients living in Labrador-Grenfell were related to the likelihood

of being seen by a nephrologist less frequently than those living in other health

regions.

Table 11: Poisson loglinear regression analysis of factors associated with number of nephrologist visits following referral; parameter estimates from SPSS output

Parameter	B	SE	95% Wald CI		Hypothesis Test			OR	95% Wald CI for OR	
			Lower	Upper	Wald Chi-Square	df	P value		Lower	Upper
(Intercept)	.348	.0414	.267	.429	70.869	1	**.000**	**1.417**	1.306	1.536
Age=18-39yrs	.384	.0354	.314	.453	117.251	1	**.000**	**1.468**	1.369	1.573
Age=40-49yrs	.323	.0233	.278	.369	192.787	1	**.000**	**1.382**	1.320	1.446
Age=50-59yrs	.337	.0160	.305	.368	440.783	1	**.000**	**1.400**	1.357	1.445
Age=60-69yrs	.174	.0131	.149	.200	177.073	1	**.000**	**1.190**	1.160	1.221
Age=70+yrs	0ᵃ							**1**		
Sex=Male	.210	.0108	.189	.231	376.826	1	**.000**	**1.233**	1.208	1.260
Sex=Female	0ᵃ							**1**		
Diabetes status=Yes	.081	.0110	.059	.102	54.014	1	**.000**	**1.084**	1.061	1.108
Diabetes status=No	0ᵃ							**1**		
ERIHA	.597	.0374	.524	.670	255.355	1	**.000**	**1.817**	1.688	1.955
CRIHA	.230	.0421	.147	.312	29.824	1	**.000**	**1.258**	1.159	1.367
WRIHA	.527	.0382	.452	.602	190.282	1	**.000**	**1.694**	1.572	1.826
G-Labrador	0ᵃ							**1**		
Avg_eGFR<15	1.396	.0345	1.328	1.464	1634.290	1	**.000**	**4.039**	3.775	4.322
Avg_eGFR<30	.835	.0187	.798	.871	1989.222	1	**.000**	**2.304**	2.221	2.390
Avg_eGFR<45	.294	.0178	.259	.329	274.352	1	**.000**	**1.342**	1.296	1.390
Avg_eGFR<60	-.074	.0178	-.109	-.039	17.374	1	**.000**	**.929**	.897	.961
Avg_eGFR>=60	0ᵃ							**1**		
Kidney function=Unstable	-.115	.0293	-.172	-.057	15.334	1	**.000**	**.892**	.842	.944
Kidney function=Stable	0ᵃ							**1**		
(Scale)	1ᵇ									

*Dependent Variable: Frequency of nephrologist Visits; Model: (Intercept), Age, Sex, Diabetes status, RIHA, Avg_eGFR, Kidney function stability; a. Set to zero because this parameter is redundant. b. Fixed at the displayed value; B=Beta coefficient; SE=standard error; df=Degree of freedom; OR=odd ratio; CI=Confidence interval; Avg eGFR= Average eGFR; RIHA=Regional Integrated Health Authority; ERIHA=Eastern RIHA; CRIHA=Central RIHA; WRIHA=Western RIHA; G-Labrador=Labrador-Grenfell RIHA

3.11 Status of referral to a nephrologist for CKD patients

Eight thousand eight hundred and fifty CKD patients were referred to nephrologists by family physicians over the study period from 2011 to 2015. Patient referral was determined when a patient with CKD appeared to have been seen by a nephrologist.

Among those with CKD stage 3a, younger CKD patients composed the largest age-group (35.4%), while those aged 40-49 constituted 27.2% of the CKD stage 3a group (Table 12). Those aged 70+ constituted the smallest age group at 14.3% of the CKD stage 3a group. It is noticed that the lower the eGFR the greater the proportion seen by a nephrologist across all age groups and irrespective of gender and diabetes.

More male CKD patients were referred to nephrologists than were female CKD patients in all stages [Stage 3a, (18.9% vs 14.2%), Stage 3b (41.4% vs 31.7%), Stage 4 (71.1% vs 57.5%), and Stage 5 (84.2% vs 78.4%)].

Diabetic patients at CKD stage 3a or above tended to be referred more compared to CKD patients without diabetes (19.3% vs 14.0 at stage 3a, 38.9% vs 31.6% at stage 3b, 65.0% vs 59.1% at stage 4, and 81.3% vs 79.2% at stage 5).

Table 12: Proportion of NL CKD patients (at given characteristics) referred to a nephrologist by stage.

	eGFR$_{MDRD}$ (ml/min/1.73m^2)			
	<15	<30	<45	<60
Age groups, 18-39	100.0	100.0	72.7	35.4
40-49	100.0	87.8	68.1	27.2
50-59	100.0	84.6	59.4	17.5
60-69	88.9	82.6	46.6	15.9
70+	74.4	56.0	28.6	14.3
Sex, Male	84.2	71.1	41.4	18.9
Female	78.4	57.5	31.7	14.2
Diabetes status, Yes	81.3	65.0	38.9	19.3
No	79.2	59.1	31.6	14.0

*all numbers are presented as %; eGFR=estimated glomerular filtration rate measured in ml/min/1.73m^2

3.12 Proportion of CKD patients receiving nephrology service within their own region

Considering nephrology service delivery by health region, 90% of CKD patients from ERIHA are seen by a nephrologist within their region of residence. By contrast, many CKD patients living in other heath regions have been seen by a nephrologist in a hospital located in another health region. 74.3%, 68.6%, and 64.1% of CKD patients from CRIHA, WRIHA and Labrador-Grenfell RIHA, respectively, were only seen by a nephrologist in their respective regions. This means the rest, 10%, 25.7%, 31.4%, and 35.9% of CKD patients from ERIHA, CRIHA, WRIHA and LG RIHA, respectively, were seen elsewhere to have a nephrologist visit or have seen other specialists like general internal medicine specialist.

3.13 As requested by the patients' partners, we looked at the following

3.13.1 Distribution of CKD in Indigenous community

In the Labrador-Grenfell health region, 1,239 patients were recorded as identifiable CKD patients from a total population of 37,229. In this database, forty-six communities from Labrador-Grenfell health region were recorded based on the patients' postal code information. As the data do not specifically identify people as being of Indigenous origin or not, the community of residence was used as a proxy for Indigenous status. Three large communities (Labrador city with a population of 9,228, HVGB with 8,109, and St. Anthony with 2,418) were analyzed separately, representing a

majority (over 78% on average) Caucasian population. The coastal communities, with a combined population of 9,282, were analyzed together, where over 85% of the population was Indigenous on average. Of this latter group, only 133 (1.4%) were documented as identifiable CKD patients. Whereas 7.5% (181), 1.7% (140), and 0.9% (79) of the population were identifiable CKD patients in Caucasian majority St. Anthony, Happy Valley-Goose Bay and Labrador city, respectively.

Age was a significant factor in CKD prevalence for the Indigenous population: the rate of CKD increased with age. Among the Indigenous CKD patients, half of them (50.3%) were in the 70+ group and 31.6% and 13.3% were in the 60-69 and 50-59 age groups, respectively. In comparison, in Labrador city, only 24% of CKD patients were aged 70+. In the other two large cities, St. Anthony and Happy Valley-Goose Bay, the proportion of CKD patients aged 70+ was similar to the proportion of those aged 70+ in the Indigenous communities at large (49.7% and 43.6%, respectively).

Females comprised 59.7% of Indigenous CKD patients and males comprised 40.3%. Among the non-Indigenous CKD patient population from St. Anthony, Labrador City and HVGB, 69.6%, 57%, and 63.6% were female, while 30.4%, 43%, and 36.4% were male, respectively.

47% of the Indigenous CKD population were suffering from diabetes mellitus, while 43.1%, 39.2%, and 46.4% of the non-Indigenous CKD patient population from St. Anthony, Labrador city and HVGB, respectively, were diabetic.

When considering the 5-year average eGFR, half of the Indigenous CKD patients fell into CKD stage 3a, 22.8% into CKD stage 3b, and 6.2% into CKD stage 4.

3.13.2 Proportion of people with diabetes tested for CKD

From 2011 to 2015, in Newfoundland and Labrador, 76,692 diabetic patients were recorded. 40,465 individuals were identifiable as CKD patients by CKD operational definition. Among them, 16,663 individuals had both diabetes and CKD. The first line screen for diabetes is a urine protein test. Among diabetic patients, only 12.8% (9,790 individuals) patients were tested for urine albumin creatinine ratio which demonstrated a huge gap in CKD screening services in diabetic patients. On the other hand, only 4.5% of CKD patients had urine analysis done which is an underutilization of urine testing, a key investigation that the care providers are not doing.

3.14   Outcomes of patient engagement

Patients' partners were not actively involved in accessing the CKD data. We sent out the thesis to all of them and asked if they had any comments or questions or if they think that we should meet and discuss their concerns. To this point, none have provided any feedback about what they believe the data have shown. This could mean any number of things; e.g. they did not read the thesis, they read the thesis but did not

understand it, or, they did not have any comments or questions. We will contact the

patient partners and try to engage again to discuss their impressions.

Chapter 4: Discussion

4.1   Introduction

This study estimates the prevalence of chronic kidney disease in the province of

Newfoundland and Labrador, Canada. To the best of our knowledge, this is the first

study to describe CKD prevalence over a 5-year (2011-15) period in the province. Our

analysis showed a relative agreement with Statistics Canada. Also, results are consistent with

other reported population-based studies[23,125] although the assessments among other

studies have variations due to their different settings and varying CKD definitions and

identification methods.

In our study, we identified CKD cases based on eGFR values only. An eGFR below

60 ml/min/1.73m^2 at two points, at least 3 months apart, was considered indicative of

CKD. Urine analysis, another valuable marker for CKD identification, was not taken into

consideration because the relevant digital data was difficult to analyze due to the

variable methods of urinalysis and the relative infrequency of urine studies.

4.2   Summary

Chronic kidney disease is an ongoing health concern in NL. This study describes

recent CKD prevalence, as well as the gaps in kidney care (i.e. lack of nephrologist visits

and risk identification testing). Understanding what demographics were best able to

access proper nephrology services will help with future planning to provide kidney care access in high-risk health regions. The study observed the regional differences in accessing kidney care. The CKD patients from Labrador-Grenfell health regions experience from the least likelihood of nephrologist visits compared to the other health regions. For those with unstable kidney function, it was found that there was a 10% lower chance of having frequent nephrologist-visits (OR=0.9, CI: 0.8-0.9, p<.0001), compared to those with stable kidney dysfunction. An Underutilization of combined eGFR and urine tests was found for targeted CKD cases among diabetic patients. Only 12.8% of diabetic patients have been tested for their urine albumin-creatinine ratio, which demonstrates a huge gap in CKD screening services for diabetic patients. On the other hand, only 4.5% of CKD patients had a urine analysis done. We found the CKD prevalence among the Indigenous community troubling. We may have only seen the tip of a bigger CKD population as a much smaller number of people with CKD were identified in the Indigenous community compared to Caucasians. This finding demonstrates that we may need to focus on CKD screening first and identify people with CKD among the Indigenous population.

4.3   Management of CKD

It is important for healthcare providers to identify patients with unstable CKD and provide an early referral to a nephrologist for a better outcome. Considering kidney function stability, the ERIHA, CRIHA, and Labrador-Grenfell health region each showed

huge potential gaps in care where only 22.2%, 15.5%, and 20.9% of unstable CKD

patients were seen by a nephrologist, respectively. By contrast, in WRIHA, 60.3% of

unstable CKD patients were seen by a nephrologist; this reflects the most efficient

referral by family physicians among the four health regions (Table 7).

Results showed that diabetic individuals, who had significantly unstable kidney

function, had a significantly higher chance of seeing a nephrologist (Table 8). When we

considered the frequency of nephrologist visit, Statistical analysis (Poisson analysis)

showed that unstable CKD patients were not visiting nephrologists more often than

stable CKD patients (Table 11). Progressive CKD patients had 10% lower chance to have

frequent nephrologist-visits (OR=0.9, CI: 0.8-0.9, p<.0001) as opposed to those with

stable kidney dysfunction. This appears to be an inefficient pattern of care.

Nephrologists, on the other hand, should be able to identify whether a patient has

stable or unstable kidney function and consider this in choosing to follow up the patients

frequently.[126] But in reality, they may not bring the progressive patients back for frequent

visits. This odd pattern of kidney care from practitioners needs attention.

4.4   Factors influencing referral to nephrologists

Consistent with previous studies[127], we found that family physicians

preferentially refer younger people with CKD to nephrologists. Analysis showed that,

compared to older CKD patients, a higher proportion of young people with a low eGFR

has been seen by a nephrologist within the first and second year after CKD

identification. This might be clinically appropriate if younger people are given more

priority because they have a greater risk of longer-term consequences than an older

person. The same is true for diabetic patients.[128] More diabetic patients with CKD have

been seen by a nephrologist within the first two years than those without diabetes. It

should be equally likely for both men and women with CKD to be referred to and seen

by a nephrologist. In our findings, male individuals were more likely to have

nephrologist visits than female individuals (8.4% vs. 6.7% in the first year and 12.2% vs

9.9% in the 2nd year, after CKD recognition).

4.5   Kidney care services and CKD

The study revealed regional variations in the average frequency of nephrologist

visits within the province. Patients living in St. John's in ERIHA are far less likely to be

seen by a nephrologist within 1 and 2 years after CKD recognition (7% and 10%,

respectively), compared to patients living in Corner Brook in WRIHA (21% and 31%,

respectively).

This study is intended to identify gaps in kidney care service. One potential gap

in service is that the CKD patients are not seeing a nephrologist, while referral at early

CKD stage plays an important role[129] in CKD management. We found that only 35.4% of

CKD patients aged 18-39 were referred to a nephrologist at CKD stage 3a (Table 12).

Only 19.3% of diabetic patients were referred to a nephrologist at CKD stage 3a.

Another gap might be in the management of unstable kidney function decline. The study found that patients with unstable CKD living in the Central health region have a much lower chance of seeing a nephrologist than unstable CKD patients living in the Western health region. Only 21.8% of CKD patients see a nephrologist in NL (compared to 21.7% for non-Hispanic white individuals in USA in 2012[130]). It is possible that the actual number of individuals with CKD in the general population is much greater than the number of individuals with CKD who have been referred to a nephrologist.

The higher rate of nephrologist visit frequency in the Western Health Region may be due to the fact that the nephrologists practicing in this region also practice internal medicine and thus may see their patients more often to deal with other health conditions. Given that there are two nephrologists in the western RIHA, and that they make up about 20% of the Internal Medicine specialists there, GPs in the region will choose to refer to them more often. By contrast, in St. John's, for example, GPs choose to refer to a cardiologist, internal medicine specialist etc. instead if they wish.

Some people who are unstable may not see a nephrologist frequently. Among different health regions, there are differences in number of CKD patients referred and frequency of nephrologist visits. We do not know the optimum proportion of CKD patient to be seen by a nephrologist. So it is possible that in WRIHA, nephrologists may be over practicing compared to other health regions or vice versa.

Many CKD patients were not seen within their respective health region according to their residence. 25.7% of CKD patients from CRIHA, 31.4% from WRIHA and 35.9% from Labrador-Grenfell health regions were receiving the nephrology services from other health regions compared to 10% of CKD patients from ERIHA. Clearly, this lack of nephrology services does not meet the required kidney care need in place, except ERIHA (10%) or they could had seen by other specialist like general internal medicine specialist. There is no nephrologist practicing in CRIHA and Labrador-Grenfell RIHA. One nephrologist from St. John's periodically travels to clinics in CRIHA and LG-RIHA. Another nephrologist travels to clinics in only Labrador City once a year. This makes it arguable that there are enough CKD patients there to justify at least one nephrologist in each health region.

Healthcare providers are not using the best information they have to risk stratify patients. Only 4.5% of CKD patients and 12.8% of diabetic patients had urine albumin creatinine ratio test done. This is very low and inhibits using a predictive score to identify kidney disease. This may also mean that GPs are not picking the highest-risk patients either to refer or follow more closely. We recommend more urine analysis both for diabetics and CKD screening procedures. We may also need to do albumin creatinine ratio test to fully understand the patients' kidney condition by using a risk stratification matrix.

**4.6	Age distribution among patients identified with CKD**

We found that, depending on the age group, older people in Labrador city are at a lower risk of having CKD than older people elsewhere. However, this finding may not be viable. This statistic may not indicate the nature of disease, but rather, the nature of the population structure of this particular city[131]. In Labrador city, of those with CKD, most are middle aged. Older people after retirement tend to leave the city, meaning that there are fewer older CKD patients there. If we looked at all the sick people in Labrador City, they largely will be middle aged individuals because they have not yet left the city. While, generally, all older people, including those who become sick and/or retire, tend to leave the city.

**4.7	Gender and sex-based analysis and identified bias**

We acknowledged the differences of prevalence of CKD between men and women. The same pattern can be observed in an end stage kidney disease treatment across the country as evidenced by CORR data. The CORR data [Appendix E] on dialysis mirrors our finding that men tend to have more progressive CKD than women.[132] CORR shows only end stage kidney disease, but this is only the tip of the iceberg of CKD. Dialysis patients across the country all show the same pattern whereby more men are recognized with kidney disease than women. This may not be a distinctly socio-cultural phenomenon but simply be that a higher proportion of people reaching end stage

kidney treatment are men. It is not that women are under-diagnosed or under-treated. There is no reason to believe that there is a bias that leads family physicians to select men over women for treatment. If there are more men than women with CKD anyway, then we can simply assume that men are at risk. This is different to experience of women versus men receiving health care in general.[133]

4.8 Prevalence of CKD among the Indigenous population

The populations of St. Anthony, Labrador City and Happy Valley-Goose Bay are mixed (mostly Caucasian); but, along the coastline of Labrador, cities/towns (e.g. Natuashish and Sheshatshiu) the population is predominantly Indigenous. Thus, if we discuss the prevalence of CKD there, we discuss the prevalence of CKD among people of Indigenous origin. Any communities other than St. Anthony, Labrador city and HVGB were considered a potentially Indigenous population. To draw conclusions about Indigenous populations, we simply left out the towns with mixed populations and higher proportions of Caucasian individuals.

We grouped all largely Indigenous communities in Labrador and identified the proportion of this group with chronic kidney disease. This is not a prospective survey; when discussing prevalence, we are dealing with what we already know. We are not sure how many people actually have kidney disease in real time; we only know how many of them we have identified based on the existing test results. There can be

differences between the actual number of patients with CKD and the number of those identified as CKD patients. Thus, we must be careful not to say that there are fewer people with CKD from the Indigenous community; that is, we only know that fewer people with CKD were identified. Lower CKD prevalence in Indigenous communities may indicate that problems are not accurately being recorded in the EMR. It may be due to the way where the information is captured, or there are not enough blood tests done by primary care providers to diagnose CKD. For that, we may need to do more blood work to understand the bigger problem. For example, Sheshatshiu, an Innu community close to Happy Valley-Goose Bay, has a very large number of people on dialysis and thus, it is probable that it also has a large number of people with CKD. Within the Indigenous population, and especially those living in remote locations, the real issues are access to care, early diagnosis, and the possibility that individuals diagnosed with kidney disease will have to leave their community for care.

4.9   Study limitations

People with two consecutive eGFRs below 60 ml/min/1.73m^2 at least 3 months apart were identified as CKD patients. This operational definition is a bit arbitrary as we ignored urinary protein and the eGFRs itself can be inconsistent. Because of the way that this analysis has been conducted, errors are possible since we may misclassify people at different points of time. While all people in the dataset met the definition at

some point during the period, they may not have met the definition at all time points.

For this reason, we used patients' average eGFRs over the whole study period and

grouped people by CKD Stage by their average eGFRs per year. For example, if we say

that someone is in CKD stage 4, we mean that their average eGFR was within the range

of 15-29 ml/min/1.73m^2 for that particular year, or for the whole period of time.

Moreover, Urine analysis (proteinuria/albuminuria) was not taken into account

to define CKD in this study because of the limited availability of the relevant electronic

medical data due to the variable methods of urinalysis. This relates to the ascertainment

bias in which many CKD patients were not included, or less likely to be included in the

study database. This unavoidable systematic distortion of the data restricted the exact

representation of CKD prevalence in the province.

There is a possibility of under- or over-testing certain age groups, relative to one

another. This could affect our understanding of the proportions of the CKD patient

population composed by different age groups. The study may not really document the

prevalence of CKD as much as it documents the prevalence of potentially recognizable

CKD. This is important because changes in patterns of ordering blood tests, in

accordance with developments in policy and associated guidelines, will also change the

apparent frequency of CKD.

The limitations associated with the retrospective study design limit the reliability

of the study results. The retrospective aspects of this kind of administrative data may

introduce misclassification or information bias, for which the temporal relationship is often difficult to assess. However, such a large population dataset like that included in this study indicates that there will be some definitive evidence concerning CKD prevalence.

The data entirely depends on lab reports. Errors could have occurred (eg. male, female coding error) and there is no way of knowing if or how often such errors occurred. Thus, any of the data fields could contain errors, and we do not really know the likelihood of this. With regards to the laboratory values of eGFR and claim ascertainment, we acknowledge that there were up and down swings in the eGFR values. We acknowledge that there are some rather extreme values that seemed improbable from the clinical point of view that we chose to leave out of analyses as these are a very small proportion of the whole data set.

Any conclusion we have reached is based on the analysis of the vast majority of cases; this minimizes the limitation of missing information.

In the analyses, the smaller communities were ignored as there were insufficient cases to draw conclusions about them. One of many analytic challenges regarding small data from the remote communities was that the low accessibility of the population made it problematic to see the actual picture of CKD prevalence. The issue with the small data from remote communities is a barrier to addressing persistent unsolved research in many of the public health challenges including CKD.

Using secondary data causes limitations as there may have been errors with the initial recording or in the transfer to the study database. There are two common errors found in retrospective laboratory test data reviews: measurement errors, which are made in the recording of continuous variables, and misclassification errors, which are made in the recording of categorical variables. Measurement errors may be widespread when serum creatinine as a measurement of kidney function is not measured with the same calibrated scale for each individual in different communities. Indeed, different health regions were reporting kidney function in different mnemonics, such as Creatinine, GFRMDRD, EGFRC, EGFRCALC, etc.

Prevalence of CKD in the first year (year of 2011) was not complete, as eGFR laboratory test results were recorded starting from April of that year instead of from January, 2011. Individuals were grouped into five age categories (18-39, 40-49, 50-59, 60-69, and 70+ years) based on their age at the baseline year 2011 and this was not changed year by year. This means that as people aged >70 years passed away, they were not replaced by people who were 69 years old in 2011.

Some people who truly have CKD would have a single final creatinine in 2011 while others would have a single first creatinine in 2015. Both were excluded from the original data due to not meeting the case definition and may cause an artefact.

One of the issues of 'Ecological Fallacy' is the confusion between individual correlations and ecological correlations. In this study, we used Labrador coastal

communities as a proxy of being Indigenous and interpret group level data on the individual level. If, as part of the CAN-SOLVE-CKD initiative, the results of this study are utilized to contribute to a larger prospective study of greater duration and geographical distribution covering the whole of Canada, this limitation will be avoided.

Other markers of care such as blood pressure, use of appropriate medications to reduce CKD progression and cardiovascular benefit (ACEi/ARBs, statin) are not included in the analysis as these data were not available. NLCHI does not capture the blood pressure data as it is an in-office reading. When EMR becomes the norm, we may have blood pressure records in the database in the future. There was no active pharmacy network data (record of medication data) at the time of the study period, i.e., between 2011 and 2015, which would have allowed us to include use of appropriate medication in the analysis.

4.10   Significance of findings

The results of this study may be utilized to contribute to a larger prospective study of large duration and geographical distribution that will cover the whole of Canada as part of the CAN-SOLVE-CKD initiative. Ultimately, the hope is to utilize the results in pre-emptive evidence-based planning and development for healthcare services and research studies that will enhance resource utilization and cost effectiveness in the provision of kidney care services in NL.

The goal of this project is to improve kidney care delivery for individual and population level CKD management with the aim of improving outcomes and quality of life for CKD patients and reducing overall healthcare costs for populations with CKD by reducing hospital admissions and procedures (e.g. dialysis). These improvements will be based upon the establishment of spatially enabled kidney care data structures that facilitate the performance of province-wide area analyses. Such applications are as follows: CKD surveillance; kidney care access using network analysis; community health profiling to address nephrology service delivery and healthcare disparities for CKD patients living in the underserved communities within the province. This provides both patients and providers with a greater understanding of the factors that affect the kidney health status of targeted populations. Keeping this in mind, this patient-oriented study would allow both patients and healthcare providers to be more aware of CKD than at any time in the past.

Distributing this information may facilitate early diagnosis and intervention, and increase the awareness of kidney disease and its prevention. Finally, a decrease in CKD incidence and a reduction in exposure to various risk factors may improve patients' quality of life and decrease societal burden and health-care costs.

4.11   Conclusions and recommendations

We have reached a number of conclusions based on what we have observed in the data. We concluded that there are differences between regions in CKD prevalence. There is limited access to specialist kidney care in NL. People who have more progressive disease were not seeing a nephrologist more often compared to the people with non-progressive CKD. Our recommendation is that the nephrologists should review their re-booking decision making. Further, we also found that kidney specialty services in NL are poorly distributed geographically. Some people with CKD need to see a nephrologist from other health regions to receive kidney services. One strategy to minimize this gap in care is to employ a nephrologist in the Central regions. The population size in CRIHA justifies having a nephrologist on the ground, rather than their being dependent on the outreach clinic. In other regions (WRIHA and Grenfell-Labrador health region), the density of CKD patients is not sufficient to justify having more nephrologists. However, to serve their needs, distance methods such as e-consults, telehealth, etc., could be enhanced.

There is an under-utilization of urine testing. This indicates a need to adopt the risk stratification method to observe patients' CKD status. We need to determine whether this is a result of a knowledge gap amongst primary care practitioners or resistance from the patient; this could be a question to address in a future research context. The answer to this question will probably drive the intervention. For example: if the low testing rate is a result of a knowledge gap, continue medical education might

work to increase uptake of proteinuria/albuminuria testing in primary care in NL. These

are all actionable, relevant, and impactful findings that could lead to improvements of

care. Their most important potential impact is to incite future changes in kidney care.

Kidney care in Newfoundland and Labrador refers to the planned use of

nephrology service resources that respond in real time to kidney problems.[134] We

recommend further work in this regard on spatial GIS analysis that includes 'spatial

auto-correlation', 'hotspot analyses' and 'network analyses'.

Practices adopted in the province at the moment are focused mostly on a

passive approach that waits for patients to visit a kidney care center. Robert et al.[135]

concluded that referral of all CKD patients to nephrologists is impractical. There are only

11 nephrologists in NL according to a 2015 report by the Canadian Medical Association

(CMA).[136] CKD is being managed mostly by primary care providers following available

guidelines. We need a system for early detection in high risk groups that screens CKD

patients at the primary care level by integrating interdisciplinary services and employs

appropriate management strategies (e.g. greater use of urine protein measurements to

risk stratify, visualization tools to see change in kidney function over time, prompts to

refer to a nephrologist in a timely manner etc.). Another option includes increasing the

number of nephrology outreach teams. These teams seek CKD patients around the

province and provide evidence-based kidney care delivery at a reasonable cost.

Outreach programs are important especially for underserved communities in remote

locations and communities in which individuals have difficulties accessing proper care.[137] With telehealth, patients in remote communities may benefit from nephrologist access, regardless of location.[138] Telehealth allows remote communities to receive the care required, first to identify and then to manage CKD. Also, electronic consultation (eConsult) may allow primary care providers direct access to a nephrology consultant to assess the right course of action for CKD patients, avoiding unnecessary referrals.[139] It also increases access to kidney care services at the point of care.

More research is needed to understand the interaction between kidney care and geography such as regional influences, care disparities within remote communities etc. To improve health outcome in remote communities, we need to make sure that we take into account the specific challenges that these population face, considering the impact of social determinant on health among and within each of these groups; while we advance our understanding of the unique needs of each health region. From an awareness perspective, the public recognition[140] of the seriousness of CKD and how it leads to ESKD is important.

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Appendices

Appendix A: Invitation to all practicing nephrologists in NL asking permission for data use

Dr. Brendan Barrett MB, MSc, FRCPC
Professor of Medicine (Nephrology)

(On behalf of Dr. Mohammad A. Hossain, MBBS
Masters student, Dept. of Clinical Epidemiology
Memorial University of Newfoundland)

Dear colleagues,

I am in the process of putting together a project that would look to map the density and location of CKD cases in the province as a whole. This can be done using existing lab datasets available at the Centre for Health Information. They have lab data from 2011 to 2015. In addition to mapping where those with the problem live I would also like to map where and when they are seen by a nephrologist. That could be done by linking to fee for service claims. We would not be using any identifiers for any of this, however given there are only 10 or so nephrologists in the province and knowing where everyone works, it would be hard not to know who seeing people was. The overall aim here is to identify pockets of disease within the province that are not accessing nephrology services with a view to subsequently starting an exploration of different ways to address any gaps identified.

I would like to seek your permission to do this work given that you are part of the small group of nephrologists.

If you have any comments on this project, please let me know. If you generally approve and would be willing to let this proceed as outlined, please let me know by reply to this email.

Thanks.

Looking forward to hearing from you.

Appendix B: Estimates of population (2011 Census and administrative data), by age group and sex for Newfoundland and Labrador, Regional Integrated Health Authorities 2011-2016

Geography	Year	Total, all ages	18-39	40-49	50-59	60-69	70+
NL	2011	525,037	141,935	81,389	85,554	67,816	53,384
	2012	526,450	140,709	80,470	85,649	70,693	54,961
	2013	527,409	139,635	79,020	85,793	73,049	56,913
	2014	528,333	138,591	77,415	85,810	75,350	58,995
	2015	528,676	137,250	75,650	85,725	77,386	61,178
ERIHA	2011	313,618	91,560	48,017	49,286	38,416	29,570
	2012	315,647	91,438	47,661	49,523	40,225	30,325
	2013	317,567	91,679	46,927	49,755	41,586	31,493
	2014	319,622	91,892	46,169	50,013	42,983	32,678
	2015	321,008	91,640	45,533	50,092	44,243	33,888
CRIHA	2011	94,972	20,855	14,921	16,620	14,234	11,990
	2012	94,650	20,208	14,721	16,533	14,751	12,394
	2013	94,062	19,526	14,426	16,446	15,190	12,795
	2014	93,576	18,876	14,121	16,323	15,567	13,219
	2015	93,221	18,391	13,661	16,294	15,906	13,673
WRIHA	2011	79,218	18,472	12,295	13,971	11,340	9,371
	2012	78,823	18,069	11,964	13,954	11,713	9,699
	2013	78,519	17,611	11,640	13,922	12,129	10,006
	2014	77,967	17,159	11,256	13,811	12,509	10,355
	2015	77,457	16,807	10,730	13,721	12,804	10,733
LGRIHA	2011	37,229	11,048	6,156	5,677	3,826	2,453
	2012	37,330	10,994	6,124	5,639	4,004	2,543
	2013	37,261	10,819	6,027	5,670	4,144	2,619
	2014	37,168	10,664	5,869	5,663	4,291	2,743
	2015	36,990	10,412	5,726	5,618	4,433	2,884

Source: Statistics Canada, CANSIM table 109-5355; (retrieved February 16, 2018)

Appendix C: Indigenous population proportion by community in Labrador-Grenfell health region, 2016

Percentage of aboriginal population by community/census subdivision, Labrador-Grenfell Health, 2016

Community Name/Census Subdivision	Percentage
Anchor Point	3.0
Bird Cove	11.1
Cartwright	86.0
Census Subdivision = 1009001, including Croque and St. Juliens	22.2
Census Subdivision = 1009021, including Bear Cove, and other communities	9.1
Census Subdivision = 1009031, including Ship Cove and other communities	4.9
Census Subdivision = 1009032, including Gunners Cove and St. Lunaire-Griquet	4.3
Census Subdivision = 1010001, including Capstan Island and L'Anse Amour	20.0
Census Subdivision = 1010008, including Battle Harbour	81.1
Charlottetown, Labrador	81.0
Churchill Falls	20.0
Conche	0.0
Cook's Harbour	9.1
Englee	3.5
Flower's Cove	0.0
Forteau	37.7
Goose Cove East, Northern Peninsula	5.7
Happy Valley-Goose Bay	46.6
Hopedale	93.0
Labrador City	8.8
L'anse au Clair	34.0
L'anse au Loup, Labrador	12.6
Main Brook, Northern Peninsula	8.1
Makkovik	86.8
Mary's Harbour	59.4
Mud Lake	96.3
Nain	92.4
Natuashish	95.7
North West River	64.5
Pinware	13.6
Port Hope Simpson	90.2
Postville	88.6
Raleigh	0.0
Red Bay	22.2
Rigolet	95.1
Roddickton-Bide Arm	9.2
Sheshashiu	98.5
St. Anthony	9.8
St. Lewis	74.4
Wabush	11.3
West St. Modeste	10.3

Appendix D: Patient's Partner Invitation Letter

Dr. Brendan Barrett MB, MSc, FRCPC
Professor of Medicine (Nephrology)

(On behalf of Dr. Mohammad A. Hossain, MBBS
Masters student, Dept. of Clinical Epidemiology
Memorial University of Newfoundland)

Dear <Patient Partner's Name>

I contacted the Kidney Foundation to see if they might be able to find people with an interested in being involved in some kidney related research. They provided your name.

If you are interested please let me know by reply. I would also need to know if you are comfortable with being identified to others who may have a similar interest through all of you collectively working together with me and a graduate student.

Thanks for considering.

Appendix E: Adult incident dialysis patients, selected characteristics, Canada (excluding Quebec), 2008 to 2017

Table 9 Adult incident dialysis patients, selected characteristics, Canada (excluding Quebec), 2008 to 2017

Modality	Characteristic	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
HD	Mean age (years)	65.0	65.3	65.1	64.9	64.7	65.4	65.0	65.0	64.6	65.1
	Age 65+ (%)	56.5	57.3	56.0	56.7	55.5	57.0	56.0	56.7	55.9	57.7
	Male (%)	60.2	59.7	60.3	62.4	62.7	62.6	62.0	62.7	60.7	61.5
	Diabetes (%)	47.5	50.4	52.4	54.2	53.9	54.0	56.1	56.1	55.4	56.8
	Mean comorbidity index*	1.9	2.1	2.0	2.2	2.1	2.0	2.1	2.2	2.1	2.0
	Mean BMI	28.2	28.4	28.4	28.3	28.9	29.2	29.0	29.3	29.1	29.3
	Mean eGFR[†]	10.3	10.7	10.6	10.6	10.4	10.3	9.9	10.1	10.3	10.1
	Late referral (%)[‡]	36.3	36.5	34.4	33.8	30.6	31.9	31.8	30.8	31.4	30.3
PD	Mean age (years)	61.1	62.1	62.1	61.1	62.0	61.4	61.6	62.1	62.9	62.2
	Age 65+ (%)	45.1	46.0	47.3	43.7	46.1	45.3	45.4	48.8	50.6	50.1
	Male (%)	55.9	58.4	59.7	60.5	60.2	60.7	58.5	61.6	67.4	65.0
	Diabetes (%)	43.3	45.6	48.7	46.8	52.6	50.3	52.7	53.9	54.1	54.1
	Mean comorbidity index*	1.1	1.1	1.3	1.2	1.2	1.1	1.3	1.2	1.4	1.2
	Mean BMI	27.7	28.2	27.5	27.5	28.0	27.5	27.9	28.1	27.9	28.0
	Mean eGFR[†]	10.6	10.8	10.9	10.2	10.0	9.9	9.5	9.5	9.4	9.6
	Late referral (%)[‡]	10.4	10.1	8.9	10.2	7.0	7.7	7.4	7.7	7.5	6.9

Notes:

* The index assigns each of the 14 comorbid conditions collected in CORR a weight from 1 to 10. The possible range is from 0 to 32.
† Estimated glomerular filtration rate (eGFR) as determined by the Modification of Diet in Kidney Disease (MDRD) formula (mL/min/1.73 m^2).
‡ Patients who first see a nephrologist less than 90 days before starting dialysis.
BMI: Body mass index.
Data from Quebec was excluded from this table because of significant under-reporting between 2011 and 2017.
Source: Canadian Organ Replacement Register, 2018, Canadian Institute for Health Information.