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# Factors Affecting Hemodialysis Adequacy and Patient Safety

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# Factors Affecting Hemodialysis Adequacy and Patient Safety


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**Abstract**

**Background**: This study examined longitudinal data from patients in end stage renal disease (ESRD) undergoing renal replacement therapy (RRT) in the form of hemodialysis from three facilities managed by Africa HealthCare Network based in Rwanda. The objective was to understand the factors that affect dialysis adequacy and develop an informatics solution to improve outcomes.

**Methods**: Data from 4203 dialysis sessions from 96 patients was collected from September 2016 to October 2017. Dialysis adequacy was measured using a value, Kt/V that is considered the gold standard and is normally calculated at the end of each session. In this measurement, Kt/V is a dimensionless ratio representing fractional urea clearance, where K is the dialyzer urea clearance (expressed in liters per hour), t is time on dialysis (expressed in hours), and V is the volume of distribution of urea (expressed in liters). The data was transformed into a patient period dataset to aid with data analysis. Descriptive analysis of the data was performed using SAS, and data quality issues that were identified were addressed using an informatics solution.

**Results**: The study resulted in a multilevel model that explained intra and interpersonal differences in Kt/V values over time. Gender, systolic blood pressure, temperature, pulse rate, and respiration rate were found to be significant predictors of Kt/V values ($p<0.05$). The results of this research can be incorporated into the dialysis information systems to identify patients that are unlikely to receive adequate dialysis dose. This information can be leveraged by nephrologists who then are able to better outline a plan of action to improve dialysis outcomes.

**Conclusions:** Using the predictive model we were able to plot the impact of study variables on Kt/V. The plots helped visualize the changes of Kt/V values over time and interaction of the different study variables on Kt/V. The plots show the first 30 days after RRT initialization as a critical period since the Kt/V values were significantly lower and that dialysis inadequacy is common during the initial stages of RRT initialization. The study also shows the impact of an informatics solution that assists the technicians to identify data quality issues in real time will improve data quality and also improve accuracy of the model that predicts dialysis adequacy.

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# 1. Chapter I

## 1.1. Introduction and Rationale

Kidneys are the organs that filter waste products from the blood. They are also involved in regulating blood pressure, electrolyte balance, and red blood cell production in the body. Normal kidney or renal function filters toxins from the blood stream, and when renal function deteriorates, these toxins accumulate in the blood.

Symptoms of renal failure are due to the accumulation of waste products and excess fluid in the body. Patients with renal failure may demonstrate weakness, shortness of breath, lethargy, swelling, and confusion. Inability to remove potassium from the bloodstream may lead to abnormal heart rhythms and sudden death. Early renal failure may be asymptomatic, and patients may progress almost silently to chronic renal disease. Chronic kidney disease (CKD) is defined as a reduced glomerular filtration rate (GFR). The various stages of CKD are defined by the estimated levels of glomerular filtration rate (eGFR). Stage I is defined as albuminuria (albumin excreted in the urine) with an eGFR greater than 90 ml/min/1.73m2, Stage II is albuminuria with an eGFR between 60 and 90 ml/min/1.73m2, Stage III is an eGFR between 30 and 60 ml/min/1.73m2 with or without albuminuria, Stage IV is an eGFR between 15 and 30 ml/min/1.73m2 with or without albuminuria, and Stage V or End Stage Renal Disease (ESRD) is an eGFR less than 15 ml/min/1.73m2 with or without albuminuria. Untreated chronic kidney disease (CKD) almost always progresses into End Stage Renal Disease (ESRD).

Renal Replacement Therapy (RRT), commonly known as dialysis, is necessary to remove waste products such as urea from the blood when kidneys are failing (Diseases, 2017). Treatment of the underlying cause of kidney failure may result in kidney function returning to normal. If the kidneys fail completely, the only treatment options available may be dialysis or transplant (National Institute of Diabetes & Digestive & Kidney Diseases, 2017). Dialysis is the process of filtering impurities from the blood using a membrane filter called a dialyzer. While dialysis has improved over the years, it still burdensome on the patient and their quality of life. Chronic kidney disease patients require dialysis 2-3 times per week, each dialysis session lasts approximately 4 hours, and this life sustaining time commitment can be upsetting to the patients' work-life balance. Patients require lifelong dialysis unless they receive a kidney transplant. In developing nations, this problem is compounded by the fact that dialysis is expensive and costs around $230 per month while the income of 50% of the populations is about $4 per day.

There are two types of dialysis - peritoneal dialysis and hemodialysis. This study focuses on the most commonly used type hemodialysis.

### 1.2. Problem statement

Renal Replacement Therapy (RRT) or Dialysis in this situation is the process of removing excess water, solutes, and toxins from the blood in individuals whose native kidneys have lost the ability to perform these functions naturally.

The first successful dialysis was performed in 1943. Since then, dialysis technology has improved considerably with few complications. However, patients undergoing dialysis are at increased risk of cardiovascular disease (David W. Johnson, 2009). Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). To reduce morbidity and mortality, it is important to ensure adequate dialysis.

"Adequate dialysis" is interpreted as the amount of dialysis required to keep a patient alive and relatively asymptomatic. Since the inception of hemodialysis, there have been numerous approaches to quantify the delivered dialysis dose in a reproducible manner and to link the dialysis dose with clinical outcomes. (Ankit N. Mehta & Andrew Z. Fenves, 2010)

Two methods are generally used to assess dialysis adequacy, URR and Kt/V. URR stands for urea reduction ratio, which refers to the reduction in urea from dialysis. URR measure how effectively a dialysis treatment has removed waste products from the body and is commonly expressed as a percentage. URR is usually measured only once every 12 to 14 treatments.

Kt/V is another way of measuring dialysis adequacy. Kt/V is a dimensionless ratio representing fractional urea clearance, where K is the dialyzer urea clearance (expressed in liters per hour), t is time on dialysis (expressed in hours), and V is the volume of distribution of urea (expressed in liters). (Ankit N. Mehta & Andrew Z. Fenves, 2010)

According to National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Kt/V is more accurate then URR in measuring how much urea is removed during dialysis. In this study we use Kt/V to measure dialysis adequacy because it is measured at sessions, unlike URR.

Dialysis guidelines have recommended single pool Kt/V > 1.2 as the minimum dose for chronic hemodialysis (HD) patients on thrice weekly HD. If Kt/V values are lower than 1.2, necessary steps can be taken to improve Kt/V values. Since the V value for a patient does not have a lot of variability, Kt/V can be improved either by increasing K or t.

Multiple studies have shown that Kt/V alone does not explain higher mortality, but it is still considered the gold standard in measuring dialysis adequacy. Future research should focus on collecting additional data attributes that do not rely on expensive tests and can explain the causes of sudden death and higher cardiovascular mortality among the ESRD population. Aline C. Hemk et al conducted a study using data from the European Renal Association– European Dialysis and Transplant Association (ERA-EDTA). They developed a prediction model for long-term renal patient survival based on only four predictors - age, primary renal disease, sex, and therapy at 90 days after the start of renal replacement therapy. The concordance index, indicating the discriminatory power of the model, was 0.71 in the complete ERA-EDTA Registry cohort and varied according to country level between 0.70 and 0.75. Even though the type of primary renal disease is not included in our study data, it can be included in future studies. The reliance of the model on only four predictors makes it very practical and valuable in Rwanda where the majority of the patient population cannot afford expensive tests. If this model performs adequately in the East African population, it would be very useful to nephrologists who want to forecast patient survival.

The cost of dialysis treatment in United States is covered by Medicare with a small coinsurance. Medicare has well defined reporting requirements, and this results in providers keeping track of all data attributes to meet these requirements. In the U.S., donor kidneys for transplantation are not readily available and therefore 77% of ESRD patients require maintenance dialysis.  In resource constrained countries in sub-Saharan Africa, the patient bears the majority of the cost of dialysis. It has been estimated that only 1.5 % of those requiring renal replacement therapy in sub-Saharan Africa receive RRT (Anand, 2013). The available resources and lack of reporting requirements have a direct impact on the quality of data collected. Most of the dialysis provider databases maintain what is captured by dialysis machines along with the patient vitals.  National registries are required to study the prevalence and treatment outcomes and prevent underreporting.

Data quality impacts every decision along the patient care continuum. Poor data quality increases healthcare costs and also negatively impacts patient safety. Recognizing data quality as more of a human challenge than a technological challenge will empower training programs to ensure data that can provide insights into patient care.  An informatics solution that assists the technicians to identify data quality issues in real time will help address the technological portion. To address the human aspect of data quality employee training and data governance programs are required. Unlike business data, healthcare data quality checks have to be non-intrusive to patient care; therefore, the human aspect of data quality is more important than enforcing data quality through technological solutions.

## 1.3. Primary Outcome

The dialysis information system deployed at African Health Network calculates the Kt/V values at the end of each session. These Kt/V values are available in the data set and will be used to study dialysis adequacy and its association with other variables in the data. If KTV values can be predicted using the values collected during the dialysis session, and quantify the factors affecting dialysis adequacy, appropriate action can be taken to ensure adequate dialysis. An informatics solution can allow for useful extraction of data points during dialysis so that patient care can be improved. .

## 1.4. Purpose statement

Unmanaged chronic kidney disease (CKD) progresses into end stage renal disease (ESRD). Even though the prevalence of chronic kidney disease has not increased, there is evidence that the number of ESRD cases has increased (Kiberd, 2006). In keeping with the rising demand for hemodialysis, there has been an increase in the number of dialysis centers. With growth in the patient population, quality of care needs to be standardized and maintained without impacting efficiency. If hemodialysis does not have the necessary quality, level of blood toxins and patients' clinical symptoms will not be properly controlled and morbidity and mortality rate will increase (Ali Tayyebi, 2012).

This research is conducted using data from a resource constrained setting. Variables that are routinely measured in developed nations are not available in this study. In the future, with improved data collection the predictive power of the model can be improved with the increase in sample size and the inclusion of additional useful variables.

The data captured during the dialysis session are critical to measuring dialysis adequacy either by using a formula or predicting Kt/V values before the session is complete. The dialysis staff is trained to capture required data elements for each session, but it is observed that 25% of the sessions are missing key data elements. This paper will outline an informatics solution to identify and address data quality issues and improve patient care.

## 1.5. Research questions

The intent of this research is to answer the following research questions.

- Can we identify the factors that affect dialysis adequacy and use this to improve patient care?
- Is there an association between a drop and increase in blood pressure during the session to dialysis outcomes?
- How can we improve data collection and data quality to improve patient safety using an informatics solution? Informatics is the science of how to use data, information and knowledge to improve human health and the delivery of health care services (AMIA, 2011).

## 1.6. Definition of Key Terms

**Glossary**

| **Term** | **Definition** |
|---|---|
| CKD | Chronic Kidney Disease |
| ESRD | End Stage Renal Disease |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| HD | Hemodialysis |
| Hb | Hemoglobin |
| SPB | Systolic Blood Pressure |
| DBP | Diastolic Blood Pressure |
| MAP | Mean Arterial Pressure |
| Sp02 | Oxygen concentration |
| COPD | Chronic obstructive pulmonary disease |
| GFR | Glomerular filtration rate |
| RRT | Renal Replacement Therapy |

# 2. Chapter II

## 2.1. Literature Review

Literature search was conducted on PubMed, African Journals Online, the WHO Global Health Library, and Web of Science between Jan 1, 2000, and Dec 22, 2017. The search strategy combined terms in two broad themes of hemodialysis and outcomes: the former included hemodialysis, hemodialysis dose, and such MeSH headings as renal replacement therapy, the dialysis adequacy measure intradialytic hypotension and dialysate temperature, the latter included Kt/V, Urea Reduction Ratio and Urea Kinetic modeling. To support the informatics approach to improving data quality, literature review topics also included the broader topic of data quality in Electronic Medical Records (EMR) systems instead of just dialysis information systems.

Published studies on dialysis outcomes used by healthcare providers in different settings and factors affecting outcomes were reviewed. Peritoneal and at-home hemodialysis that is not the focus of this study was excluded. The following terms illustrated in Table 1 were used to conduct the public health literature review:

**Literature Review Search Terms**

**MeSH Terms:**
1. Hemodialysis
2. Kt/V
3. CKD
4. ESRD
5. URR
6. Dialysate
7. Hypertension
8. Intradialytic Hypotension
9. Kinetic Modeling
10. Dialysate Temperature

**Text Terms:**
1. "Dialysis Adequacy"
2. Dialysis outcomes
3. Chronic kidney Disease
4. EMR Data quality
5. Dialysis information system
6. Kinetic Modeling
7. Nephrology Information system

The search narrowed down 50 research papers that addressed factors affecting dialysis outcomes measured using Kt/V values and papers highlighting the importance of data quality in research.

## 2.2. State of existing research

The documented prevalence of ESRD in Sub Saharan Africa is lower than in the U.S. and European countries. This is likely explained by the fact that there is a significant portion of population that are not counted due to lack of access to healthcare. Even among those with access to care the cost of RRT is a financial burden and a large percentage of patients discontinue treatment and subsequently die. Patients are often unable to afford the cost of lab tests which are routinely done in the U.S. Of the data attributes that are captured for every session, blood pressure is one of the most important factors, the increase or decrease of which is frequently observed in most of hemodialysis patients during dialysis. Fluctuation in blood pressure contributes to numerous complications and hemodialysis intolerance in patients, thereby significantly effecting dialysis adequacy (Mottahedian Tabrizi E, 2009).

The Hemodialysis Study also known as HEMO study is a multi-center, prospective, randomized, clinical trial designed to evaluate the efficacy of the dose of dialysis delivered (standard v high) and dialysis membrane flux (low versus high) in reducing the morbidity and mortality of patients. Depner et al. studied dialysis dose and effect of gender and body size on the outcomes of dialysis using the Hemodialysis Study dataset. He found that women had a 19% lower mortality risk (Thomas Depner, 2004).

A previous cross-sectional study aimed at investigating the relationship between blood pressure and dialysis adequacy found no linear association between blood pressure and the indices of dialysis adequacy (Ali Tayyebi, 2012). This study concluded that other effective factors such as pre- and post-dialysis level of urea play a more significant role in the adequacy of dialysis. This study included 100 patients but a limitation of this study was that it was using cross sectional study to research longitudinal data with repeated measurements over time.

Blood pressure changes during the dialysis session and increase in cardiovascular mortality have also been studied. One study found that patients whose blood pressure changed significantly after hemodialysis had a higher risk of mortality. Difference in systolic blood pressure, hemoglobin concentration, Kt/V and albumin were also identified as independent risk factors for all-cause mortality in hemodialysis patients. (Jiayue Lu, 2017)

There are patient care parameters that are currently not being captured in the databases and that require critical and conservative interpretation. Many historical analyses of intradialytic changes in blood pressure were based solely on the difference between baseline readings taken before initiating hemodialysis treatments and final readings taken after the treatment had been completed. These analyses were limited because of the omission of fluctuating changes that occur during dialysis; however, the information gleamed from these previously unstudied data points and the implications on interventions are often ignored and uncertain (Mahesh Krishnan*, 2012). Our study data contains intradialytic observations of blood pressure, temperature, respiration and heart rate that were recorded every 15 minutes. Studies have shown the temperature reading taken during the session has an impact on dialysis outcomes. A systematic review that studied the effects of reducing dialysate temperature concluded that reducing dialysate temperature lowered the incidence of intradialytic hypotension (McIntyre, 2006). This process is called cool dialysis and the applicability of this procedure in place of standard dialysis need to be studied in the future as this study data contains sessions with large intradialytic pressure variations.

Another important factor affecting dialysis adequacy is the time on dialysis denoted by t in the formula for Kt/V. However, time on dialysis has not received the importance it deserves due to the impact of longer dialysis session on patient morale and quality of life. During normal hemodialysis practice the session is prolonged only if it is unavoidable. There have been multiple publications addressing the importance of treatment time. The results showed longer dialysis sessions correlated to lower hospitalization rates. But, short high-efficiency HD has become the norm. Balancing dialysis time and patient convenience is almost an art instead of science.

Respiratory symptoms are usually underestimated in patients with chronic kidney disease undergoing maintenance hemodialysis. A study “Impact of Hemodialysis on Dyspnea and Lung Function in End Stage Kidney Disease Patients” by Anastasios et al investigated the prevalence of chronic dyspnea and the relationship of the symptom to lung function indices. They concluded that dyspnea is a major symptom among the CKD population, and symptoms improve after hemodialysis. (Anastasios F.Palamidas, 2013). Our dataset does not capture indices of lung function, but respiratory rate as an indicator of Dyspnea is captured through the dialysis session and impact of respiration rate on Kt/V is part of the study.

Hypotension is one of the most acute complications of dialysis treatment. Identifying and treating hypotensive episodes is critical to dialysis tolerance. Bradycardia commonly known as slow heart rate can cause blood pressure drops during dialysis sessions. The threshold for identifying a hypotensive episode is defined as a drop in mean arterial pressure of more than 20 percent. (C. Zoccali, 1997) . Changes in heart rate greater than 5 beats per minute constituted tachycardia or bradycardia. The dataset has heart rate readings through the dialysis session, which allows an examination of the impact of this variable on dialysis outcomes.

## 2.3. Data quality and Information technology

The use of information technology to improve patient care continues to be a laudable goal in the health sector. As electronic health record (EHR) systems have become more widely implemented in all healthcare settings, the need for information governance (IG) is greater than ever. To meet these advanced challenges, rigorous information and data governance, stewardship, management, and measurement is fundamental. (Davoudi, Dooling, & Jones, 2015). Structured data quality reports developed in the EMR system and feedback sessions with the service principals has shown to improve data quality. (Taggart J, 2015). Data quality is critical to patient care as poor data quality is implicated in treatment errors, repeated lab tests, and missed diagnoses. When the quality of data is higher, the ability to make a strong recommendation for or against an intervention dramatically increases. Lack of interoperability in healthcare information systems increases the need for manual re-entry of data and adds additional points of failure within the data supply chain and remains an obstacle in today's healthcare information technology landscape. In this study we analyze the data flow and integration points within the dialysis network and provide an informatics solution to improve data quality.

## 2.4. Summary

Existing literature on the factors impacting dialysis adequacy have found associations between intradialytic hypotension and cardiovascular events.  Temperature control using low dialysate temperatures has been showed to reduce large changes in intra-dialytic blood pressure readings. Renal replacement therapy is associated with higher mortality, and patients with chronic obstructive pulmonary disease and asthma are at higher risk of heart failure.  Renal failure can compromise respiratory function in many ways. Acute pulmonary edema is the most common and severe complication in renal failure patients. Furthermore, the presence of fluid in the pleural and abdominal compartments can restrict thoracic expansion, leading to changes in the ventilatory mechanics and gas exchange (Fernanda Maia Lopes, 2013). Other studies identify dyspnea, commonly known as shortness of breath, as an important symptom of CKD and improves after hemodialysis. Measuring and monitoring intra-dialytic respiratory rate is critical in identifying patients who are at increased risk. Changes in heart rate during dialysis is associated with hypotension and makes this an important study variable. The previous studies reviewed here analyzed the impact of each of these factors in detail. In this paper, studying the combined effect of all the factors on dialysis outcome is the purpose of this research.

# 3. Chapter III Methods

## 3.1. Introduction

The objective of this thesis is to identify the factors that are associated with dialysis adequacy and provide feedback to the dialysis technicians to ensure adequate dialysis dosage. Incomplete or incorrect data quality makes it difficult to measure dialysis adequacy and improve patient safety. The informatics portion of this thesis will outline a solution to detect and notify dialysis staff about data quality issues in critical data attributes that contribute to patient safety. The challenge of introducing additional steps into the dialysis workflow without impacting patient care and efficiency is also discussed.

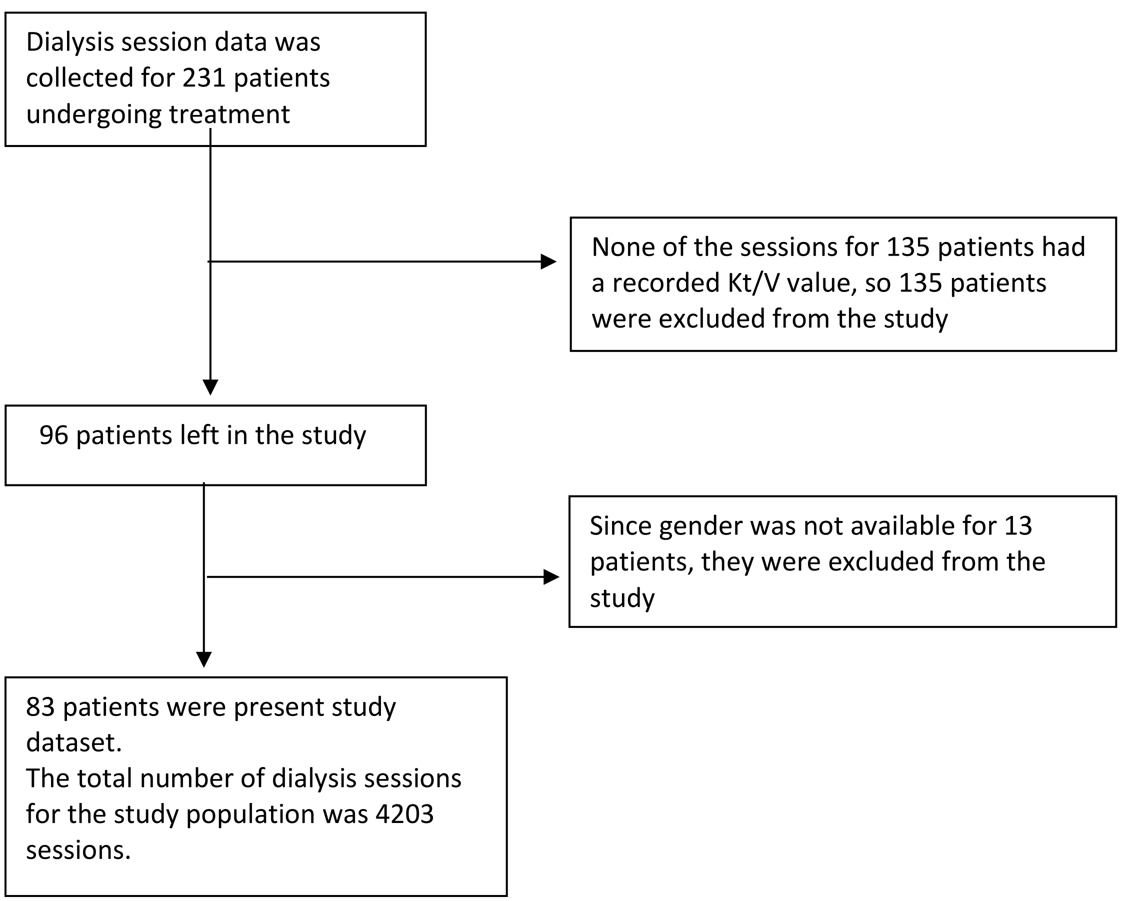
To determine dialysis adequacy, two methods are currently used. The simplest marker is the urea reduction rate (URR) for which only the pre- and post-dialytic blood urea concentrations are needed. However, the use of URR does not consider the effects of ultrafiltration on urea removal or the effect of urea generation during dialysis. Kt/V is another method of measuring dialysis adequacy and is a dimensionless ratio representing fractional urea clearance, where K is the dialyzer urea clearance (expressed in liters per hour), t is time on dialysis (expressed in hours), and V is the volume of distribution of urea (expressed in liters) (Ankit N. Mehta & Andrew Z. Fenves, 2010)

The Kt/V is more accurate than the URR in measuring how much urea is removed during dialysis, primarily because the Kt/V also considers the amount of urea removed with excess fluid.

## 3.2. Population and Sample

This study examined longitudinal data from ESRD patients undergoing dialysis from three facilities managed by Africa HealthCare Network based in Rwanda. The EMR system used by the provider is Clinicea[R]. The data was collected during each dialysis sessions. Dialysis session data for patients were collected over the period starting from September 2016 to September 2017. The number of sessions a patient underwent varied based on when the patient started treatment, number of sessions per week, and treatment compliance. The number of sessions ranged from 5 to 250 sessions per patient.

Sample size for the study



The mean age of patients in the sample was 52.6 years with a standard deviation of 14.3, 19% of the patients were female, 80 % male and no gender specified for 13% of the patients who were excluded from the study. The data were transformed to a single record per dialysis session. Both hypotension and hypertension being important risk factors for patient safety additional variables were created using the blood pressure readings at the start and end of the session to record a drop or increase in readings during the session.

### 3.3. Research Design

This is an observational study of patients that underwent dialysis in one of the three African HealthCare Network's dialysis centers. For this dialysis network, the criteria for dialysis adequacy is set as Kt/V value greater than 1.3 which is higher than the dose recommended by NIDDK.

Along with the Kt/V values the dataset contains demographic information gender and age, patient vitals recorded at check-in and readings for systolic blood pressure, diastolic blood pressure, temperature, respiration, and pulse rate measured every 15 minutes during the dialysis session. The session readings contained blood pressure variations during the dialysis sessions and this was coded as the difference between the values at the beginning of the session and the values at the end of the session to indicate whether there was drop or increase in the blood pressure. Hemoglobin values were not consistently available for all the patients and since aggressive treatment of anemia does not result in better outcomes, hemoglobin values were not included. All patients in the sample are of African descent, so race was not included as an attribute.

Descriptive analysis was performed and the summary of demographic characteristics is provided in Table 1. Mixed effects models were constructed to analyze longitudinal data. To address the data quality issues an informatics solution was designed. This system consisted of data quality reports and real time data quality checks.

The goals of the informatics solution:

1. To assess staff understanding of the Dialysis Event Protocol
2. To assess data collection and reporting methods
3. To identify common barriers to complete and accurate data collection and reporting
4. Identifying systematic and recurrent errors that may require correction to data beyond the specific feedback provided
5. Assess and improve the quality of Dialysis Event data

The study data contained demographic information of the patient and the variables that were collected during the dialysis sessions.

Figure a: Attributes included in the data set:

| Attribute name | Description |
|---|---|
| ID | Patient Identifier |
| Age | Age in whole years |
| Gender | Gender |
| Diastolic BP | Diastolic Blood Pressure |
| Systolic BP | Systolic Blood Pressure |
| Mean Arterial Pressure | Mean Arterial Pressure |
| Pulse Rate | Pulse rate during the session |
| Respiration | Number of respiration per minute |
| Session Date | Session Date |
| Session Time | Session Time |
| Sp02 | Oxygen concentration |
| Temperature | Temperature |
| Weight Removed | Weight Removed |
| KTV | Calculated KTV value |

In the dataset, there was a field for comments, four out of the 231 patients included in the original dataset were recorded as deceased in the comments field, but this data could not be used as a comprehensive list of mortality data. The KTV values for these four patients were in the recommended range but it observed that the hemoglobin levels for the patients were lower than the rest of the dialysis population but there is not enough data to test the hypothesis that low hemoglobin levels is correlated with increased mortality so these 4 patients were excluded from the study.

## 3.4. Procedures

Structured Query Language (SQL) was utilized for scrubbing the data, an essential task prior to the analysis. Improbable values and outliers were replaced with missing values. After the scrubbing process, data quality assessment was performed, and feedback reports were provided for the dialysis network for training and implementing processes to improve data quality.

## 3.5. Statistical Analysis

**Table 1.**
Study variables included in dataset and their mean values

| Variable | Combined | Male | Female | Standard deviation |
|---|---|---|---|---|
| Number of subjects | 96 | 65 | 18 | |
| Mean age | 52 | 52 | 53 | 13.5 |
| Mean systolic BP | 156.7 | 154.7 | 159.2 | 26.9 |
| Mean Pulse Rate | 79.5 | 78.6 | 84.6 | 15.6 |
| Mean Respiration Rate | 17 | 17 | 17 | 1.8 |
| Mean Number of sessions | 4203 | 2857 | 638 | |
| Mean oxygen saturation | 98 | 98 | 98 | 2.6 |
| Mean body temperature | 36.1 | 36.1 | 35 | 0.27 |
| Mean Kt/V | 1.3 | 1.26 | 1.5 | 0.26 |

Descriptive analysis of the dataset was conducted to understand the distribution of variables. Outliers were identified and treated as missing values so they could be imputed later using SAS. All patients in the study had different dialysis schedules ranging from three times a week to once a month. For modeling this longitudinal data that did not have fixed schedule for the observations, the date of the dialysis session was converted to an integer starting from zero, the first date of the first dialysis session was coded as zero and the number of days elapsed between the first and second session was the integer value for this variable..

The individual growth model is a statistical technique widely used to examine the trajectories of individuals and groups in repeated measures data. This technique is used to analyze the changes over time of Kt/V values in this hemodialysis data set. An individual growth model estimates the average trajectory as well as individual trajectories, thus allowing for the explicit examination of inter-individual differences in intra-individual change. It readily estimates both linear and nonlinear change; it permits inclusion of individuals not assessed at all time points (Henian Chen, 2006). This method is preferred to traditional models such as repeated measure ANOVA because the standard requirements of equal numbers and intervals of assessment do not have to be met. The subsequent potentially substantial loss of information may result not only in a lowering of statistical power but also in a potentially biased subsamples used in the final analyses. The statistical maximum likelihood model used to generate the estimated effects assumes multivariate normality of the model residuals, linear relationships, and homoscedasticity and missingness at random. When the dependent variable distribution is heavily skewed, this assumption of normality may be violated. In this study, a log transformation of the original dependent variable was performed to minimize the impact of extremely large values on the analysis

Analysis showed an increase in the Kt/V values in the first couple of sessions followed by a reduction in slope. To model this change in slope a new variable was created to indicate whether the session is within the first thirty days of dialysis initiation or the session is past the first thirty days of dialysis initiation. The cutpoint of 30 days was chosen as preliminary examination of the graphical data suggests a different slope before and after 30 days. Repeated measurements during a dialysis session over repeated sessions, for more than one patient, represent a multilevel data structure. SAS procedure for mixed effects modeling was used to identify significant predictors and produce the parsimonious model.

The primary research question was to identify associations between dialysis adequacy and any of the factors available in the dataset. The data were analyzed by using a mixed effect model, and parameters were estimated using maximum likelihood (ML) estimation. This method modeled individual change over time, determined the shape of the growth curves, explored systematic differences in change, and examined the effects of covariates.

Stepwise model development. To identify variables associated with Kt\V, a stepwise regression approach was employed. Relevant predictors were incorporated into a model that included multiple Level-2 variables: measures of Systolic blood pressure were added to the model first; gender was added second; measures of temperature, pulse rate and respiration were entered subsequently. The interaction terms for each of the variable measuring the passage of time was added to the model. Improvements in model fit were evaluated by comparing fit statistics (-2 Log Likelihood statistic) across models, the model with the smallest value for AIC, AICC was chosen as the final model. We used this final model to predict Kt/V by controlling for variables and study the impact of an individual variable. A compound symmetrical structure of the within-subject covariances was also chosen.

The study resulted in a multilevel model that calculated Kt/V, the final model contained the following variables: SessiondateInt denoted the date of the session expressed as an integer starting from zero to indicate the number of days elapsed since RRT initialization, a variable early to indicate whether thirty days have passed since RRT initialization, Interaction between the two variables session date and early.

systolic blood pressure, gender, temperature, pulse rate , respiration rate, interaction between time and pulse rate , interaction between gender and early , interaction between gender and pulse rate and interaction between respiration and temperature.

Mathematical representation of the multilevel model:

Level 1 model:

$$\log(KtV) = \beta_{0i} + \beta_{1i} * sessiondateint + \beta_{2i} * early + \beta_{3i} * sessiondateint * early + \varepsilon_{ij}$$

Level 2 model:

$$\beta_{0i} = \gamma_{00} + \gamma_{01} * pulserate_i + \gamma_{02} * systolic_i + \gamma_{03} * temperature + \gamma_{04} * respiration + \gamma_{05} * female * pulserate + \gamma_{06} * temperature * respiration + \zeta_{0i}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11}\, pulserate$$

$$\beta_{2i} = \gamma_{20} + \gamma_{21} * female$$

$$\beta_{3i} = \gamma_{30}$$

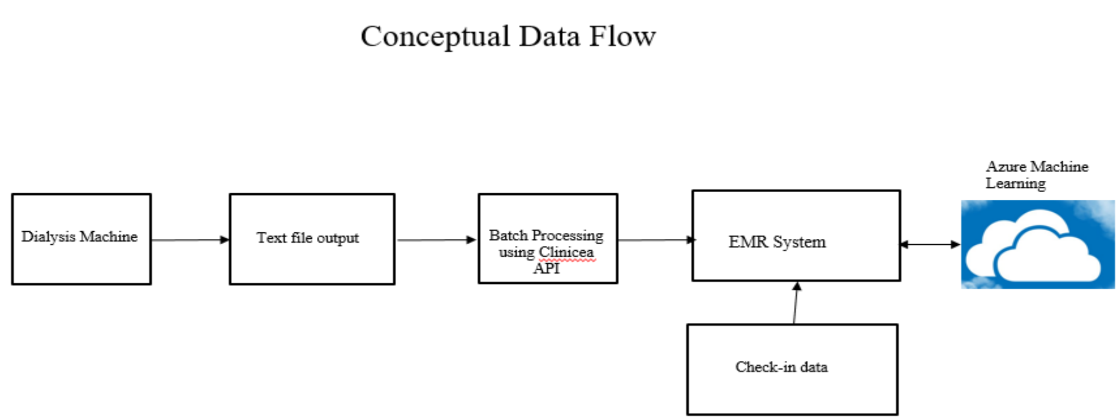
$Where\ \varepsilon_{ij} \sim N(0, \sigma^2)\ and\ \zeta_{0i} \sim N(0, \sigma^2)$

## 3.6. Data-mining techniques

The statistical analysis is done using SAS 9.4 from SAS Institute Cary, NC. For implementing the solution in the real world setting to predict Kt/V values, a cloud based machine learning platform known as Azure ML from Microsoft Redmond, WA is used. Azure ML supports R programming and simplifies the effort to convert the SAS models to R. Azure ML being a platform as a service is a cost effective approach as it provides the functionality to implement machine learning models in a production systems without dedicated hardware and expensive software licenses.

## 3.7. Data flow in the nephrology setting

High-level description of the dialysis information system within large dialysis organizations and the interactions with external databases.




**Data flow in Africa HealthCare network.** High-level description of the dialysis information system within large dialysis organizations and data flow from dialysis machines to EMR system and to and from the machine learning platform.

## 3.8. Emory University Institutional Review Board (IRB) Clearance

The details of the dataset and research procedures were submitted for Emory Institutional Review Board (IRB) review. Emory University IRB determined that the research does not require IRB review since the de-identified data set does not meet the definitions of research with human subjects.

# 4. Chapter IV Results

## 4.1. Introduction

To address the research questions, multilevel models were constructed and estimated. The factors affecting dialysis adequacy was quantified in the model and we were able to study the impact of each variable and significant interactions while controlling for all other variables. The results of this research can be incorporated into the dialysis information system to identify patients that are likely to not receive adequate dialysis. This information can be useful to the nephrologists and may outline a plan of action to improve dialysis outcomes.

## 4.2. Key findings

Gender, systolic blood pressure, temperature, pulse rate, and respiration rate were found to be significant predictors of Kt/V values. The predictors and the p values are as follows: SessiondateInt ($p<0.0001$), early ($p<0.0001$), Interaction between the two variables session date and early ($p<0.0001$), systolic blood pressure ($p<0.0001$), gender ($p<0.0001$), temperature ($p<0.0036$), pulse rate ($p<0.0001$), respiration rate ($p<0.0064$), interaction between time and pulse rate ($p<0.0001$), interaction between gender and early ($p<0.0103$), interaction between gender and pulse rate ($p<0.0097$) and interaction between respiration and temperature ($p<0.0061$).

The modeling process provided insights that were not apparent in the dataset. The model showed how the Kt/V values increases rapidly over the first 30 days of RRT initialization. After 30 days the increase is gradual. This showed that lower than the recommended Kt/V values is persistent during the initial phase of RRT initialization.

**Figure 1. Kt/V trajectory over time**

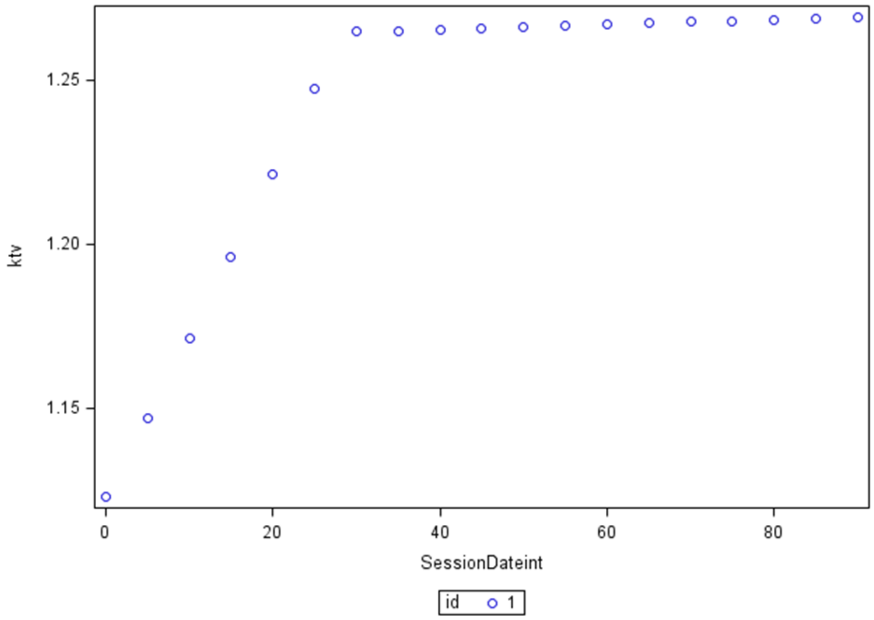
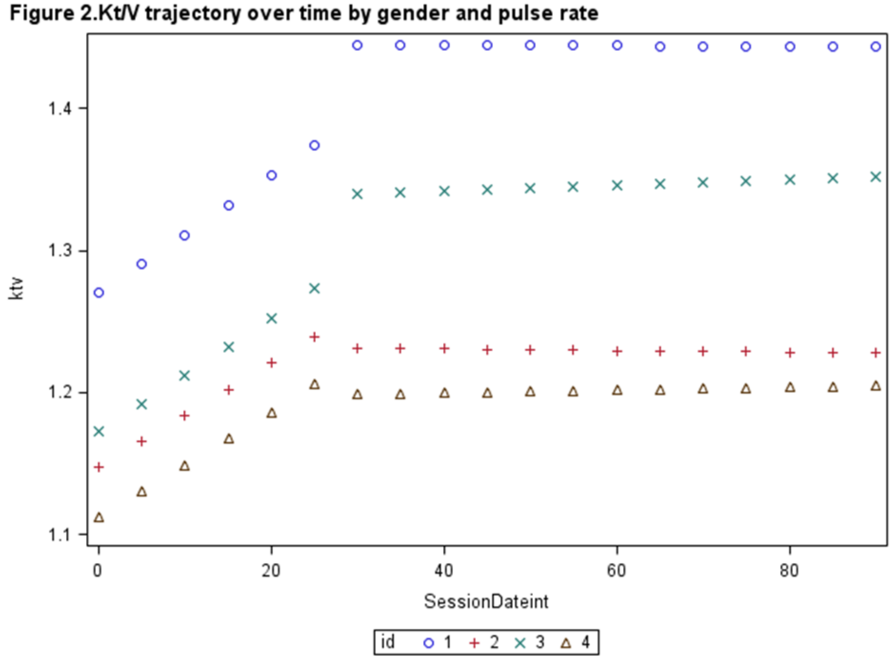



**Figure 2.Kt/V trajectory over time by gender and pulse rate**

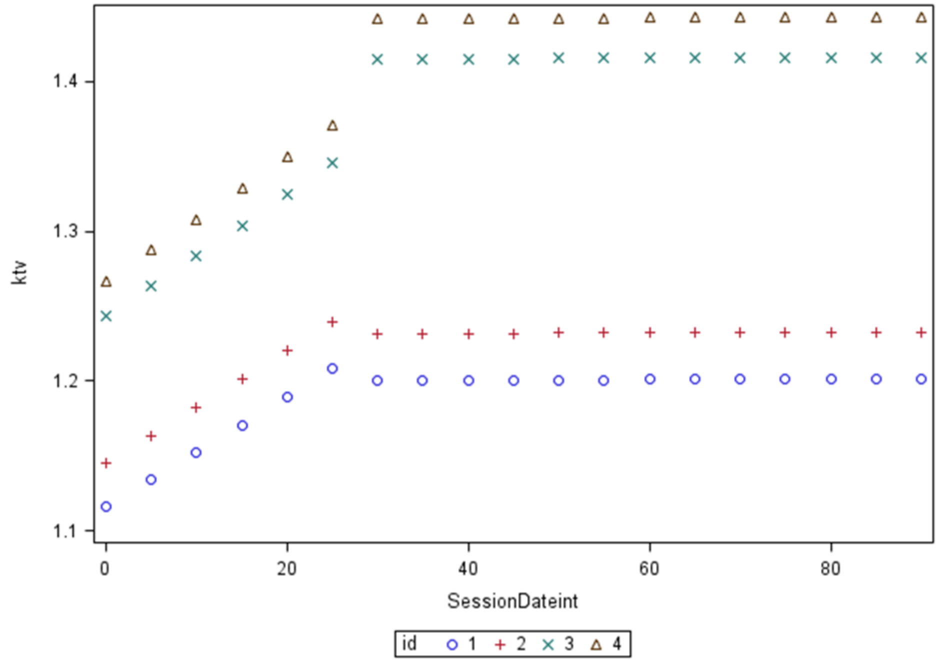



| Id | Description |
|---|---|
| 1 | Female with lower quartile pulse rate and median value for all variables |
| 2 | Male with lower quartile pulse rate and median value for all variables |
| 3 | Female with higher quartile pulse rate and median value for all variables |
| 4 | Male with higher quartile pulse rate and median value for all variables |

Figure 2 shows the significance of gender in determining Kt/V value.  Female patients and are easily able to achieve the dialysis network's target value of 1.3 for Kt/V. This is in line with the fact that men have larger body weight than women and their larger values for V which represents the volume of fluid in the body composition. Men therefore require more time on dialysis to achieve the same Kt/V values.

The interaction between gender and pulse rate is also significant. Females with a lower pulse rate have the highest Kt/V values when controlling for all other variables Kt/V values decrease with increase in pulse rate. Also, males with pulse rate in the lower quarter tend to do better than men with pulse rate in the higher quartile. Pulse rate is a significant predictor and lower heart rate is associated with higher Kt/V values. This is in line with the existing research, which associates tachycardia (increased heart rate) as a predictor of poor survival in hemodialysis patients. (Kunitoshi Iseki, 2011)

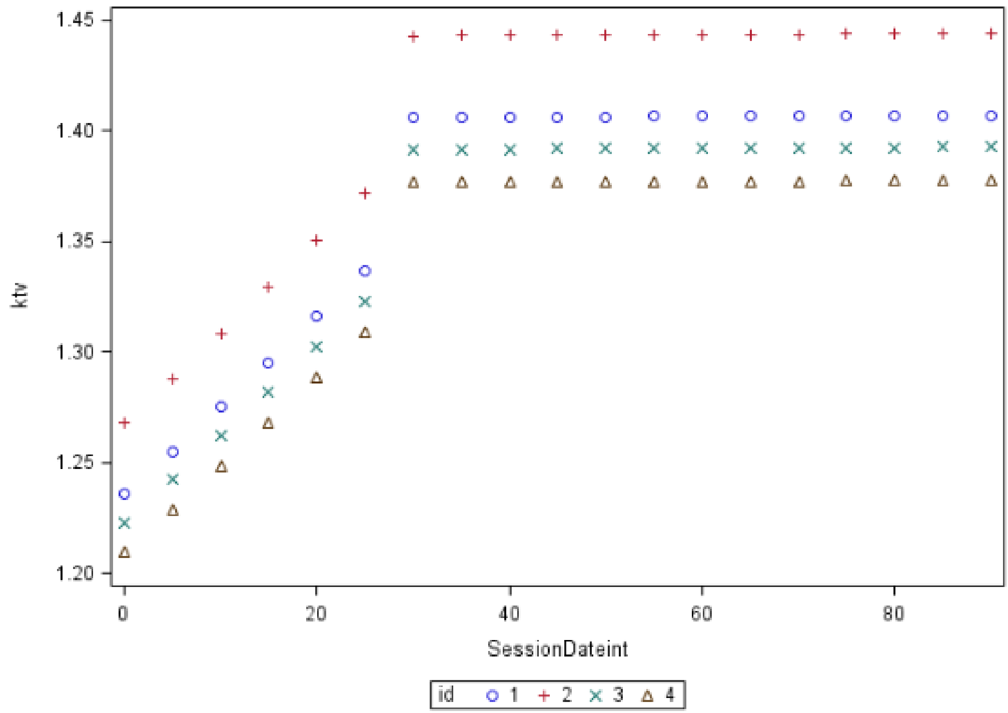
Figure 3.Ktv trajectory of systolic blood pressure quartiles




| Id | Description |
|---|---|
| 1 | Male with lower quartile systolic blood pressure and median value for all variables |
| 2 | Male with higher quartile systolic blood pressure and median value for all variables |
| 3 | Female with lower quartile systolic blood pressure and median value for all variables |
| 4 | Female with higher quartile systolic blood pressure and median value for all variables |

The systolic blood pressure and diastolic blood pressure readings at the start of the dialysis session was found to be insignificant predictor of Kt/V. However, the systolic blood pressure reading at the end of the dialysis session was a significant predictor for Kt/V. For those patients whose blood pressure readings remain in the upper quartile had higher Kt/V values compared to the patients whose systolic blood pressure readings were in the upper quartile. This needs to be further investigated as numerous studies that have shown that pressure drop causing intradialytic hypotension is a significant predictor of CVD risks.

**Figure 4.Kt/V tragectory of Temperature and respiration quartiles**




| Id | Description |
|---|---|
| 1 | Profile with lower quartile temperature and lower quartile respiration rate. |
| 2 | Profile with higher quartile temperature and lower quartile respiration rate |
| 3 | Profile with lower quartile temperature and higher quartile respiration rate. |
| 4 | Profile with higher quartile temperature and higher quartile respiration rate |

Figure 4 shows the interaction of temperature and respiration on Kt/V values. An increase in body temperature increases the baseline Kt/V values. While increase in respiration rate has a negative impact on the Kt/V values. The plot identified by id=2 shows a patient profile with body temperature in the upper quartile and respiration rate in the lower quartile. This patient profile has higher Kt/V values compared to patient profile identified by id 4 where the patient has temperature in the upper quartile and respiration also in the upper quartile. However, the rate of change of the Kt/V values over time remains unchanged regardless of the temperature and respiration rate.

### 4.3. Informatics solution

While analyzing the data flow within the dialysis network, we found that the data flow from the dialysis machines to the EMR system was manual. This manual entry of data contributed to majority of the data quality issues found in the dataset. Feedback was provided to the dialysis network to update training procedures to improve data quality. The technicians were provided training to ensure data was captured adequately.

As a short term fix to address the data quality issue, reports were developed that provided insights to the volume, type, and personnel associated with the data quality issues. Data quality reports showed overall data quality issues across the selected time frame. The staff had the ability to drill down and view monthly, weekly, daily or even to the individual entries. The ability to see data by location, by supervisor and even down to the dialysis nurse who entered the data improved accountability. The reports were used by supervisors to provide feedback to employees and provide incentives for accurate data.

For issues where the root cause was identified as human errors, the technicians who were responsible for were provided additional training. In conjunction with this, data governance policies were put in place, EMR systems were configured to alert the technician of missing data or data that is out of the valid range in order to further aid the technician in entering correct values into the user interface for data entry.

The permanent long term solution for the data quality involved automating the data transfer from the dialysis machine to the EMR system. While the manufacturer of the dialysis equipment did not support direct data transfer, the option to output text files from the data port was a viable option. The EMR system ClinicеaR by Clinicea Software, Singapore has an application programming interface (API) that allowed an external application to write data into the EMR database without manual re-entry. A program to read the text files and write data to the EMR system was designed to automate the data transfer. One of the drawback for this approach is that the transfers are done as a batch process and not in real time. However, the efficiency, data quality, and speed made this a viable solution.

The combination of reporting, training and system changes improved the data collection process. While, interactive reports showing number of missing variables and number of improbable values, provided the transparency needed to change user behavior, graphs showing the trends in data quality reinforced the team's commitment to reducing incorrect and incomplete records.

### 4.4. Other findings

Renal registries collect a well-defined set of health and demographic data from patients on RRT over many years with the aim of generating information on the causes and incidence of ESRD, and information on the prevalence, treatment and outcomes of patients on RRT. A minimum dataset would include information on the numbers of patients on each treatment modality, the numbers starting or ending treatment each year, and basic demographic information on each patient. This study shows how the lack of renal registries in the region, accurate prevalence rates require good reporting and regional registries impact data collection and reporting. Required data elements in registries also support research using geographical approach using Geographical information Systems (GIS). A GIS system would help facilitate modelling, mapping and predicting disease risks. GIS approaches can be applied to study the interplay between ethnicity, poverty, rural residence and access to RRT. Mismatching between resources and the patient population needs can be identified and interventions appropriately targeted (Rodriguez RA, 2013)

## 4.5. Summary

Systolic blood pressure readings, patient temperature, respiration rate, pulse rate and gender were all significant predictors of dialysis outcomes.  The complex interactions between these variables and time showed which patient profiles are likely to have adequate dialysis and which patient profiles need additional evaluation and adjustment to sessions to ensure adequate dialysis dose. The study showed that additional monitoring and care are needed during RRT initialization to ensure adequate dialysis before the Kt/V values have stabilized. The discontinuation rates of RRT treatment in Rwanda is higher than those in developed nations.  Improved outcomes during the RRT initialization may help treatment adherence during this critical phase.

The study also showed the state of data quality in the study settings.  Data from the dialysis organization were fragmented and it would be difficult to link patient records to out-of-facility treatments like transfusions, emergency room visits and laboratory results due to the lack of universal patient identifiers. The dialysis organization that provided study data, accepted the recommendations to improve data collections and further research. The research also highlighted the need for registries for improved public health surveillance and tracking outcomes.

# 5. Chapter V: Conclusions and Recommendations

## 5.1. Introduction

The study resulted in a multilevel model that calculated Kt/V values using readily available variables listed below:

The final model included the following variables:

1. Time elapsed since RRT initialization
2. whether thirty days have passed since RRT initialization
3. interaction between the two variables 1 and 2
4. systolic blood pressure
5. Gender
6. Temperature
7. Pulse rate
8. Respiration rate
9. Interaction between time and pulse rate
10. Interaction between gender and early
11. Interaction between gender and pulse rate
12. Interaction between respiration and temperature

The modeling process provided insights that was not apparent in the dataset. The finding that the kt/V values increases rapidly over the first 30 days of RRT sessions, then the increase is gradual. This showed the importance of stabilization of the Kt/V values during RRT initialization.

## 5.2. Limitations

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The main limitation of this study is that Individuals who cannot afford the treatment are not represented in this analysis. The second limitation was the quality of the data and lack of availability of study variables that are easily available in developed nations. The number of patient records that are usable reduced from 236 to 96 during the data validation process. Fortunately, a large volume of sessions were available for each patient. The third limitation is the lack of standardized reporting requirements affects data collection. We were unable to use possibly important variables in the analysis as measurement of these variables involves an expensive process, and therefore these variables are missing for the economically challenged patients. An example would be hemoglobin values, because anemia is an important risk factor for cardiovascular events in the CKD population, we had hoped that hemoglobin was one of the variables collected from all patients. However, more than 90% of this variable was missing in the sample; we therefore had to exclude this variable from the analysis. However, literature review shows that even though Erythropoietin-stimulating agents - Epoiten use has increased over time to aggressively correct anemia, while this approach has contributed to the revenue of dialysis networks there is not enough evidence that higher hemoglobin values are correlated with improved outcomes.

Another limitation of the study is the reliance on Kt/V value to measure dialysis outcomes. While Kt/V values are considered the gold standard for measuring dialysis adequacy, new studies show that small solute clearance and time on dialysis have a larger impact on reducing cardiovascular mortality. Without adequate data on patient survival we were unable to study the association between Kt/V values to survival. The comments in the data indicated that four patients had died without any additional details. These records had to be excluded from the study due to low number of sessions.

## 5.3. Implications

Having a model to predict the Kt/V values based on easily available data helps the staff at the dialysis centers to schedule additional time for future appointments to ensure dialysis adequacy for at-risk patients. Understanding the gender differences in achieving dialysis adequacy helps administer adequate dose for male patients for whom it is harder to reach the prescribe dose compared to female patients. Also, identifying patients who have historically large changes in pressure during dialysis can be used to improve dialysis safety and reduce hospitalizations.

## 5.4. Recommendations

To improve Kt/V, a measure of dialysis adequacy, there are three variables out of which two can be adjusted to improve outcomes. Increasing blood flow through the dialyzer. Since the dialyzer throughput denoted by K is standardized within the network, the rate of blood flow through the dialyzer is dependent mainly on good vascular access to make sure a patient is getting good clearance. The second factor is time, and increasing the time on the dialyzer is most effective but patient and dialysis facility schedules are negatively impacted. Monitoring patients for intradialytic hypotension improves patient safety during and after dialysis. The long term effects of large pressure variations on the vascular system is known to increase CV mortality. Most people on dialysis have anemia, a condition where the patients have low hemoglobin values, this is because the kidneys are not producing the hormone erythropoietin to help body make red blood cells. The benefits of anemia correction using recombinant human erythropoietin are well established. However, this dataset has sparse values for hemoglobin measurements. Also there is no information on erythropoietin use. Studies have shown the hemoglobin affects long-term survival in dialysis patients. (Avram MM, 2003). So monitoring and recording hemoglobin values are critical to patient safety. The unavailability of accurate but inexpensive diagnostic tools often precludes routine testing for anemia in low-income developing countries.

## 5.5. Data Quality

This paper shows the significance of data quality and how it affects patient safety. Most of the data quality issues were related to data entry errors or omissions. A governance process to review entered data would have identified most of the errors.

Addressing data quality is a combination of human and technology challenge. Technician training to ensure key data elements are recorded accurately is important to address the human aspect of this problem. Removing inefficient data processes like manual re-entry and also having validation and verification built into the data entry process to ensure the values entered are within range for the data attribute will address the technical aspect of data quality. The validation process checks the data against values that are probable for the patient age and gender. In range values are identified by a green data entry area. When an outlier is identified the data entry area turns red to draw the attention of the nurse to the incorrect value.

Reports were developed to show data entry errors over time. These interactive reports had the functionality to drill down to the person who entered the data. Visibility into the number of errors per person was useful for training purposes and a negative trend in the number of errors showed the organization's committed to improving data quality.

## 5.6. Conclusion

The research project involved extracting data from a dialysis information system, analyzing and cleaning the data, transforming data to an appropriate format to allow data analysis, choosing an appropriate model that addresses the research questions, using the technique of backward elimination to arrive at a parsimonious model, evaluating the final model for model fit and finally using plots to show how the primary outcome variable changes over time with respect to predictors. The study established that there is statistically significant ($p < 0.05$) association between systolic blood pressure, temperature, respiration and pulse rate along with gender and dialysis adequacy in this population. The plots helped visualize the changes of Kt/V values over time and interaction of the different study variables on Kt/V. The plots show the first 30 days after RRT initialization as a critical period since the Kt/V values were significantly lower and that dialysis inadequacy is common during the initial stages of RRT initialization. Further studies are required to study whether adjusting treatment times to ensure adequacy during the first 30 days of RRT initialization has an impact on patient survival.

The plots show that the recommended dialysis dose with values for Kt/V as 1.3 is easily achievable for female patients while male patients have difficulty in achieving this during a 4 hour dialysis session. One option would be to increase the dialysis duration for male patients. Further studies to estimate the survival rates of male and female patients will show whether the differences in Kt/V values have any effect on survival rates and whether male patients can benefit from longer dialysis sessions.

Patients with systolic blood pressure reading less than 130 mmHg had difficulty achieving the required dialysis dose. Patients whose pressure dropped more than 40 mmHg had higher values for Kt/V. However a number of studies have shown that the intradialytic hypotension was associated with high cardiovascular mortality. This shows the need to balance adequate dialysis and reduce incidence of hypotension. Reliance on KT/V values alone can have a negative impact on patient survival. These patients can benefit from longer treatment times at lower throughput to avoid these large fluctuations in blood pressure and related side effects. Further studies are needed when the dialysis information system has the minimum data attributes and requisite data quality.

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# Appendix

Variables in the model

| Description | Variable representation in model |
|---|---|
| Time elapsed since RRT initialization | SessionDateint |
| whether thirty days have passed since RRT initialization | early |
| interaction between the two variables | sessionDateint*early |
| systolic blood pressure | SystolicBP |
| Gender | Female |
| Temperature | Temperature |
| Pulse rate | Pulserate |
| Respiration rate | Respiration |
| Interaction between time and PulseRate | Sessiondateint*PulseRate |
| Interaction between gender and early | early*female |
| Interaction between gender and Pulserate | female*PulseRate |
| Interaction between respiration and Temperature | respiration*Temperature |

SAS code

```
SAS code for final model

proc mixed data=viju method=ml nobound ;
class id;
model logktv =
sessiondateint early female PulseRate systolicBP Temperature respiration
Sessiondateint*Early
Sessiondateint*PulseRate
Early*Female
Female*PulseRate
respiration*Temperature
/solution;
random intercept /sub=id type=un;
run;
```

Calculating Kt/V values using coefficients from the model

```
Formula with values for all coefficients

ktv=
exp(
        -8.7198+SessionDateint*-0.00048
        +early*(-0.07216)
        +female* 0.2940
        +PulseRate*(-0.00143)
        +SystolicBP*0.000626
        +Temperature* 0.2472
        +respiration*0.4744
        +SessionDateint*early*0.003140
        + Sessiondateint*PulseRate * (6.397/1000000)
        + early*female*(-0.05676 )
        +female*PulseRate* (-0.00178 )
        + respiration*Temperature *(-0.01314 )

) ;
```