Effect of Renal Replacement Therapy on Acute Kidney Injury in Sepsis Patients

by Peniel N. Argaw

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ABSTRACT

According to the Centers for Disease Control and Prevention, there are approximately 1.5 million cases of sepsis and over 250,000 resultant deaths each year [1]. One of the major effects of sepsis is organ failure, notably in the kidneys, lungs, liver, and brain. In the case where the kidneys fail, renal replacement therapy (RRT) may be performed in order to sustain the functionality of the kidneys and overall ameliorate patients' outcomes. The goal of this work is to determine the relationship between undergoing RRT and patient outcome. The Philips-MIT eICU Collaborative Research Database was used to identify patients with sepsis and acute kidney injury, and split the cohort into those who had undergone RRT and those who did not. Multivariate logistic regression and propensity score analysis were utilized to evaluate the treatment effect on mortality. The patients who underwent RRT had a significantly better outcome than those who did not (odds ratio = 0.260465, 95% confidence interval = 0.211568 to 0.320664, $p<0.001$). From the filtered patients, the percentage of men to women increased with those who underwent RRT (55.08% vs. 53.78%) as well as the percentage of African Americans (25% vs. 15.63%) and Other (5.86% vs. 4.04%) ethnicities. In addition to gender and ethnicity, other covariates such as Sequential Organ Failure Assessment score, cirrhosis, and metastatic cancer had a great impact on patient outcomes. This work concludes that RRT does in fact benefit the patient outcome and dialysis is a statistically significant feature within the dataset.

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Chapter 1

Introduction

1.1. Medical background

Sepsis occurs when the body reacts harshly to an infection, leading to organ failure, tissue damage, and eventually death. In contrast to many other conditions, mortality due to sepsis is caused by the immune system's response to the infection rather than the infection itself. Sepsis can start out as a treatable infection, which can lead to a fatal reaction. Therefore, diagnosing sepsis can be difficult as many of its symptoms coincide with common symptoms found in other disorders, and as a result, it may be diagnosed late in the progression of the disease.

Among important features that lead to sepsis, many factors can take part in the analysis. The most common factors are age and specific comorbidities. Sepsis has been found to be more common in younger individuals in developing countries, notably caused by malaria. Usually those of the older generation and infants tend to have sepsis in the United States. Additionally, conditions such as diabetes, cancer, and HIV have the tendency to lead to sepsis due to their effects on the immune system [2]. Although these factors can be precedents to the onset of sepsis, in many cases, it is difficult to diagnose due its complex and enigmatic nature.

A common investigation when looking at sepsis is to be able to determine mortality and the length of survival. Sepsis can be categorized into three stages: sepsis, severe sepsis, and septic shock. Patients in the sepsis stage tend to show symptoms such as fever, while patients in

severe sepsis show signs of organ malfunction, which can lead to septic shock, where the body experiences a drastic drop in blood pressure resulting in heart failure, stroke, and death [2]. Stages of sepsis can sometimes be determined by symptoms but are usually classified by likelihood of mortality. In addition to age and comorbidities, other factors such as gender, race, location of infection, and procedure types can be analyzed when evaluating likelihood of death.

One commonly used treatment for sepsis patients is renal replacement therapy (RRT), which involves replacing the kidneys' blood filtering function. The therapy includes performing dialysis, which is used to remove excess water and toxins from the blood, and creating a new filtration method using a semipermeable membrane [3]. In some more extreme cases, a kidney transplant is needed to maintain renal functionality. When evaluating for optimal performance, clinicians must consider the timing and dose of renal replacement, notably knowing when the best time to start and stop RRT on the patient and if the patient requires a continual or intermittent therapy along with the dosage amount. Although RRT is performed mainly on patients who suffer from renal failure, the therapy has also been performed on sepsis patients before their kidneys start to malfunction, although it may not directly correspond to better outcomes. To evaluate for positive effects, clinicians evaluate urine and serum creatinine levels. In most cases, if the urine output contains more that 400 mL/day of creatinine, that is a reasonable threshold to end RRT [3]. RRT may have a positive, negative or neutral effect on the patient; to evaluate the effects, important factors regarding each patient must be taken into consideration.

1.2. Project background

This work evaluates patients' health conditions detailed in a high-resolution electronic health record, the Philips-MIT eICU Collaborative Research Database (eICU CRD). The eICU CRD database is a relational database comprising 17 tables of de-identified patient stays [4]. The results are compared with similar work conducted with patient data found in an administrative health record, the National Inpatient Sample (NIS). The NIS database is a publicly available database developed for the Healthcare Cost and Utilization Project (HCUP) to record general administrative records for patients across the United States [5].

Given the eICU CRD, our goal is to evaluate the current condition of each patient and build a prediction for each respective outcome. Specifically, when looking at patients who suffer from acute kidney injury (AKI), we would like to know if performing RRT on a sepsis patient will ameliorate, exacerbate or cause no effect on the overall patient outcome. In other words, we want to compare the outcome of patients who underwent RRT with patients of similar health backgrounds who did not undergo RRT.

The eICU CRD is a dataset created to manage data across critically ill patients. The dataset contains approximately 200,859 patient unit encounters for 139,367 patients admitted to the ICU between the years of 2014 and 2015 [4]. The dataset contains multiple sub-datasets, some of them containing information on patient demographics, treatments, lab tests, hospital condition, vitals, and other administrative data, including length of stay (LOS) and outcome. The dataset also contains an Acute Physiology and Chronic Health Evaluation (APACHE) IV score used to indicate the probability of mortality in each patient based on their past 24 hours in the

ICU. APACHE IV records the reason for ICU admission, LOS before entering the ICU, the location from where the patient was admitted into the ICU, along with information if the patient underwent mechanical ventilation or emergency surgery, and the patient's age and vitals [6]. These data points are taken into consideration to evaluate each patient's score and predict a percentage of ICU mortality and estimate LOS.

We are collaborating with Dr. Barret Rush at the Division of Critical Care Medicine, in the Department of Medicine of the University of British Columbia. His contribution includes answering the same question about the effects of RRT on sepsis patients using the NIS dataset. The NIS dataset differs from eICU CRD in that it is an administrative electronic health record capturing patient information including the International Classification of Diseases (ICD-9 and ICD-10 codes), demographics, payment source, hospital conditions, and patient outcomes but is not as intricate as the eICU CRD records [5]. Our goal is to evaluate if the excess data found in eICU CRD is essential when predicting patient outcomes, or if the same goal can be achieved in an administrative dataset. Our hypothesis is that the eICU CRD will perform better than the administrative dataset due to its increased complexity.

1.3. Related works

There are several papers that have evaluated patient outcomes in populations requiring RRT. Some of the main points to consider are to realize if the treatment is necessary by looking at the current condition of the patient, understanding when to start and stop the treatment to provide the best effects, and to realize the comorbidities that may arise from RRT that can increase the risk of mortality.

In a study performed at the Universidade Federal de São Paulo, researchers evaluated two different groups of patients with acute renal failure (ARF), one who underwent dialysis and another who did not, in order to examine their respective outcomes. For this study, gender, age, comorbidities, hospitalization diagnosis, type of ARF, type of dialysis treatment, time in ICU, vitals, complications during stay, and outcome were used as input. The results showed that there were no significant differences in patient gender, age, hospitalization diagnosis, comorbidities or complications during stay. There was no difference in morbidity rates between the dialysis and non-dialysis groups, although overall, the relative death risk for the dialysis group was higher than that of the non-dialysis group. Additionally, both groups showed signs of multi-organ failure irrespective of dialysis. The main conclusion of the study was that filtering only for ARF was not as good an indicator when predicting mortality; there are other factors that will need to be considered in the patients' conditions when evaluating for mortality [7].

For example, AKI can lead to chronic kidney disease (CKD) which can increase the likelihood of death. In the Department of Internal Medicine at the University of Munich, a study was performed where patients with AKI were examined in a 10-year study to understand the effects of RRT on each patient. Their question was whether AKI leads directly to death and the development of CKD, or does AKI lead to CKD which eventually leads to death. Their results showed that patients with AKI requiring RRT showed no patterns of long-term survival. Either the patient's outcome led straight to mortality, the patient developed CKD, or the patient was deemed healthy and left the ICU only to return with the progression of CKD. The study concluded that RRT does not always lead to better results; it may sometimes lead to worsening

conditions and the onset of CKD [8]. Although the long-term outcome may lead to death, in some cases, patients were able to prolong their survival.

Survival may be prolonged by evaluating the type of RRT and finding the right time to start the therapy. A study done in the Department of Critical Care at King's College London evaluated the best factors to consider when deciding when to start RRT. They looked at various inputs, such as serum creatinine, serum urea, urine output, fluid balance, time in the ICU, and duration of AKI to provide their analysis. Their results showed that, although serum creatinine is commonly used to evaluate when to start RRT, it was not a good indicator on its own to make the decision. Rather, the results showed that urine output, specifically a low output (oliguria), an increase in fluid overload (weight gain), the number of failed non-renal organs, and the risk of further organ failure were crucial factors when deciding the right time to start RRT [9].

1.4. Motivation

The results from related studies show varying results, as RRT may lead to better or worse outcomes depending on other factors in the patient's medical conditions and the type of RRT performed. This work focuses on the impact of patients' medical conditions when evaluating outcomes, providing the opportunity to qualitatively evaluate the impact by comparing the results from multidimensional and simple databases. This work allows us to better understand how to evaluate outcomes for varying hospitals depending on their respective health records. Additionally, it provides more insight regarding the performance of the NIS dataset versus that of the eICU CRD dataset in order to prioritize important features within a patient's medical records.

Chapter 2

Materials and Methods

2.1. Database

The materials used in this work are found in the Philips-MIT eICU Collaborative Research Database (eICU CRD). For our study, we extracted the patient's demographics, comorbidities used when evaluating the scoring systems, and the scoring system values. The scoring systems used were APACHE IV, Sequential Organ Failure Assessment (SOFA), and the Charlson Comorbidity Index. The SOFA score provides a numerical evaluation of the severity and quantity of failed organs, which is notably used in evaluating the outcome of sepsis patients [10]. The Charlson Comorbidity Index provides a combined age-comorbidity value used to indicate the relative risk of mortality from each patient's associated comorbidities [11]. *Table 1.* shows the final cohort used from the eICU CRD database. In order to deal with missing values in the dataset, all patient stays containing any null data were removed from the dataset (for information on the full cohort, including those with null values, can be found in *Appendix, Table A.*). Our final cohort contains 16,376 patient stays and is evaluated on 16 features, in which the categorical features were encoding into all the same datatype. *Figure 1.* shows the flowchart to reaching to this final cohort size.

Variable	Specific variable	Without dialysis	With dialysis
n (mean (std) or specified)		15608	768
age (yrs)		66.11 (16.49)	63.94 (13.74)
gender (n (%))	Female	7724 (49.49)	345 (44.92)
	Male	7883 (50.51)	423 (55.08)
	Unknown	1 (0.01)	
height (cm)		168.30 (14.35)	167.86 (15.65)
weight (kg)		82.45 (28.70)	82.63 (25.15)
ethnicity (n (%))	African American	1428 (9.15)	192 (25.0)
	Asian	240 (1.54)	17 (2.21)
	Caucasian	12480 (79.96)	471 (61.33)
	Hispanic	620 (3.97)	32 (4.17)
	Native American	129 (0.83)	11 (1.43)
	Other/Unknown	711 (4.56)	45 (5.86)
aids		0.00 (0.05)	0.00 (0.06)
hepatic failure		0.02 (0.14)	0.04 (0.18)
lymphoma		0.01 (0.09)	0.01 (0.07)
metastatic cancer		0.03 (0.18)	0.02 (0.13)
leukemia		0.02 (0.12)	0.02 (0.14)
immunosuppression		0.06 (0.23)	0.05 (0.22)
cirrhosis		0.03 (0.16)	0.05 (0.22)
diabetes		0.23 (0.42)	0.49 (0.50)
apache score		67.74 (27.29)	71.71 (23.46)
sofa score		6.30 (3.51)	8.61 (2.94)
charlson score		4.43 (2.90)	6.21 (2.48)
hospital mortality (n (%))	Alive	13026 (83.46)	605 (78.78)
	Expired	2582 (16.54)	163 (21.22)

Table 1. Final cohort of features used from the eICU CRD database.

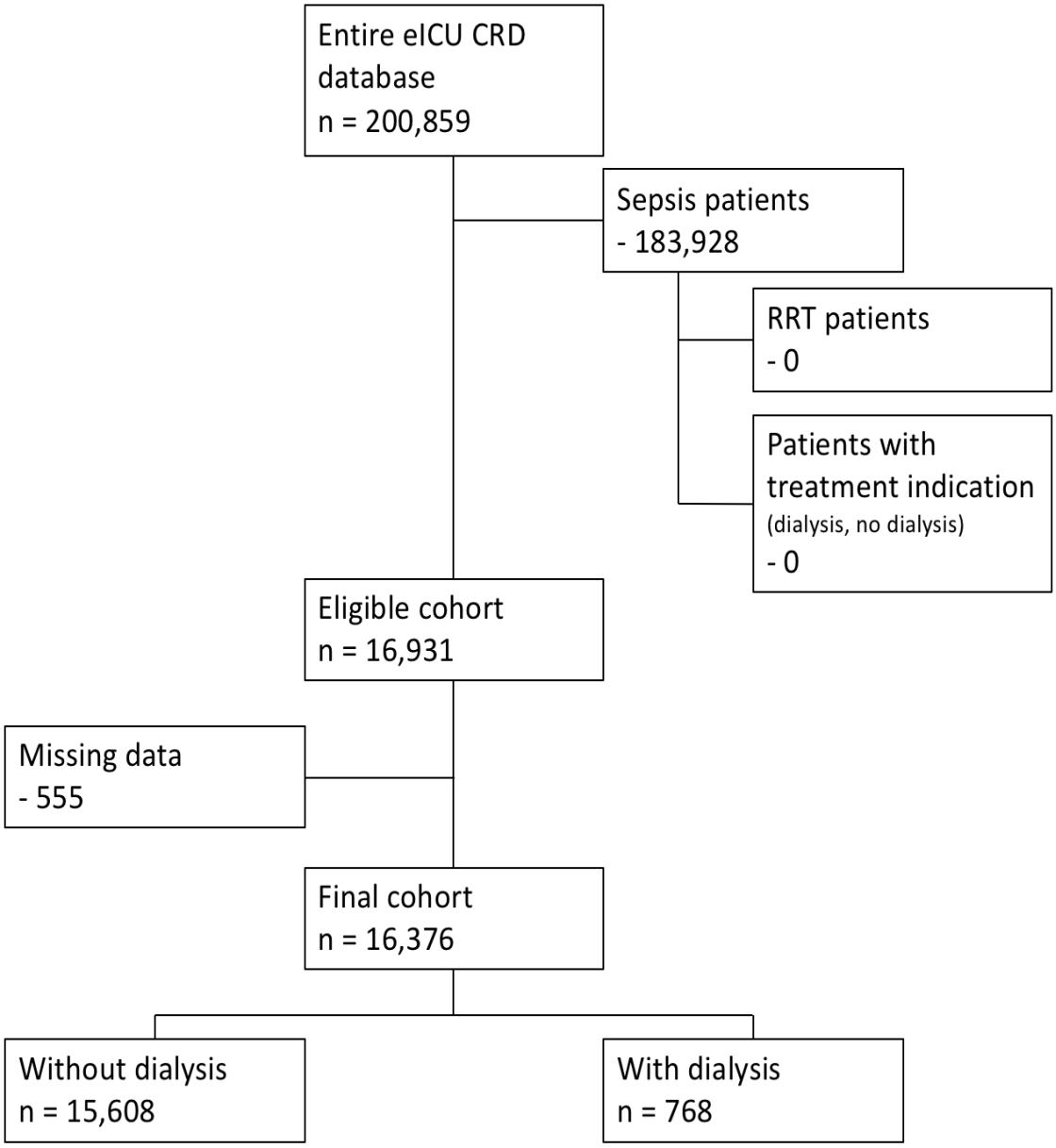

Figure 1. Cohort flowchart.

2.2. Steps

The following major steps were performed in order to obtain results on the performance of the model: feature and patient selection, data modeling, and performance evaluation.

2.2.1. Feature and patient selection

Preliminary analysis of the eICU CRD database was conducted in order to understand the type of features available and choose relevant features for the cohort. This included filtering out patients of interest: patients with sepsis, AKI, and RRT. In order to filter out patients of interest, we collaborated with medical doctors who could provide insight on the certain criteria used to determine sepsis, AKI, and RRT. In addition to patient demographics, common comorbidities, and APACHE IV, SOFA, and Charlson scores were taken into consideration.

Feature selection was selected based on previous studies. As mentioned in the Introduction, sepsis is found to be more prevalent in people who are older and have preexisting chronic health conditions. Thus, age and previous health conditions may play an important role when evaluating patient outcomes. Additionally, scoring systems have been used to provide information regarding likelihood of mortality, LOS as well as an assessment on organ failure. Another outcome to evaluate is kidney functionality as that relates to the effect of dialysis,. As discussed in the Related works section, kidney functionality after undergoing RRT may prolong survival, but may also result in worsening effects, such as CKD. Furthermore, kidney-related factors, such as urine output and creatinine levels will need to be taken into consideration when determining the current outcome of the patient. Since these metrics are taken into consideration

when calculating the SOFA score, we chose to forgo these metrics as they have already been considered in the overall chosen features. For this study specifically, we chose to omit past renal complications and dialysis treatments from the feature space; features are dependent only on current patient conditions.

Missing data points were excluded from the cohort. From a total of 16,931 patients extracted with sepsis, 555 contained null values. Additionally, all categorical features within the extracted features were encoded into float types to keep the data types of the features consistent.

2.2.2. Data modeling

Division of dataset

The eICU CRD cohort was divided into four sections: demographics, scoring systems, comorbidities, and all features. This was done to analyze the outcomes, given features within each category, and evaluate the results. The features detailed within each category can be found in *Table 2*.

Category	Features used
Demographics	Age, Gender, Height, Weight, Ethnicity, Dialysis
Scoring Systems	APACHE score, SOFA total score, Final Charlson Score, Dialysis
Comorbidities	AIDS, Hepatic failure, Lymphoma, Metastatic cancer, Leukemia, Immunosuppression, Cirrhosis, Diabetes, Dialysis
All	Age, Gender, Height, Weight, Ethnicity, APACHE score, SOFA total score, Final Charlson Score, AIDS, Hepatic failure, Lymphoma, Metastatic cancer, Leukemia, Immunosuppression, Cirrhosis, Diabetes, Dialysis

Table 2. Features found in each category.

Furthermore, the patient cohort was analyzed between the two categories: dialysis and non-dialysis. The treatment marker was indicated by a data component found in the eICU CRD database. The number of patients within each treatment type as well as their respective outcome is highlighted in *Table 3*.

Patient outcome (n (%))	**Without dialysis**	**With dialysis**
Alive	13026 (83.46)	605 (78.78)
Expired	2582 (16.54)	163 (21.22)

Table 3. Divided cohort based on treatment category.

Modeling

Once the list of relevant features and categories were created, the following step was taken to create models to analyze the correlation between the features and the outcome regarding the treatment and control groups. We used a supervised learning approach, specifically multivariate logistic regression. Logistic regression is a machine learning analysis model used to provide information regarding regression analysis in a given dataset with specific features and outcome; the regression predicts the probability of the outcome given the multiple features supplied as well as provides information regarding the impact of each feature on the outcome. In this case, multivariate regression was ran 4 times using the various features described in *Table 2.*, and the outcome was in-hospital mortality. To run this model, we used various packages within *sklearn* and *statmodels*, and this was run in a Python environment.

2.2.3. Performance evaluation

Performance of each model was evaluated using confidence intervals (CI), odds-ratios (OR), and p-values in order to understand the treatment effect.

Propensity score analysis

In addition to the regression analysis, propensity score analysis was conducted to understand the effect of dialysis. Propensity score analysis is a statistical approach used to evaluate the effect of a certain treatment or intervention versus a control group when evaluating for a specified outcome. Due to the complex nature of sepsis, there are various different features that can correspond to the condition and thus the important features may vary from patient to patient. In order to account for this variation, we calculated the score of each patient's propensity to undergo dialysis as a way to match patients in both categories: treatment and control. By matching the propensity scores with a one-to-one matching from each category, we can decrease the bias that may result from the diverse cohort. Then, this approach combined with the regression analysis, we calculated a likelihood of mortality from both the treatment and control groups.

Chapter 3

Results

16,376 patient stays were evaluated in this study. From this subset, 768 (4.7%) patients had undergone dialysis and 15,608 (95.3%) patients did not (*Figure 1.*). The likelihood of mortality for the dialysis group was 21.22%, and the likelihood of mortality for the control group was 16.54%. The likelihood of mortality for the control group from patients that matched with the treatment group was 27.21%.

Looking at the feature differences between the two groups in the entire cohort, the percentage of men was higher in the patients that underwent dialysis (55.08% vs. 50.51%), age was slightly younger within the treatment group (63.94 (+/-13.74) vs. 66.11 (+/-16.49)), and the percentage of all ethnicities besides Caucasian increased within the treatment group. For the most part, a majority of the comorbidities did not change drastically between the two, although diabetes almost doubled within the treatment group (0.49 (+/-0.50) vs. 0.23 (+/-0.42)). All the scoring systems increased within the treatment group: APACHE (71.71 (+/-23.46) vs. 67.74 (+/-27.29)), SOFA (8.61 (+/-2.94) vs. 6.30 (+/-3.51)), and Charlson (6.21 (+/-2.48) vs. 4.43 (+/-2.90)). The overall outcome showed higher mortality rates for those who had undergone dialysis versus those who did not (*Table 1.*).

3.1. Regression and propensity score analysis

Logistic regression was performed on each of the feature categories detailed in *Table 2.* in order to analyze the effects of each of the covariates.

Propensity score matching was conducted to accurately run the model on a patient population from the control group and the treatment group who had similar propensities to receive the treatment. From the 768 patients in the treatment group and the 15,608 patients in the control group, all 768 patients in the treatment group were one-to-one matched to a patient in the control group based on their propensity score for dialysis. For this analysis, the new patient population size was 1,536. The new patient cohort was evaluated using the categories detailed in *Table 2.* To see the plots of propensity score distributions for the treated, control, and matched control groups within each category, look at *Appendix, Figure B., C., D., E*. Statistical analysis using 95% CI, OR, and p-values were calculated in order to understand the effect of the treatment in the matched patient cohort compared with that in the unmatched patient cohort.

A description of the new matched patient cohort is found in *Table 4*. The evaluation on the matched patient population shows that in general most the features from the treatment and control group are matched up, though there are a few differences. There is a higher percentage of men to women in the treatment group (55.08% vs. 53.78%) and there is an increase in the percentage of African Americans (25% vs. 15.63%) and Other (5.86% vs. 4.04%) ethnicities in the treatment group. The outcome showed higher mortality rates for those in the control group, which is the opposite from the analysis on the entire cohort. (*Table 1., Table 4.*).

Variable	Specific variable	Without dialysis (matched)	With dialysis
n (mean (std) or specified)		768	768
age (yrs)		63.51 (17.36)	63.94 (13.74)
gender (n (%))	Female	355 (46.22)	345 (44.92)
	Male	413 (53.78)	423 (55.08)
height (cm)		166.93 (18.26)	167.86 (15.65)
weight (kg)		82.75 (26.96)	82.63 (25.15)
ethnicity (n (%))	African American	120 (15.63)	192 (25.0)
	Asian	20 (2.6)	17 (2.21)
	Caucasian	531 (69.14)	471 (61.33)
	Hispanic	49 (6.38)	32 (4.17)
	Native American	17 (2.21)	11 (1.43)
	Other/Unknown	31 (4.04)	45 (5.86)
aids		0.01 (0.10)	0.00 (0.06)
hepatic failure		0.03 (0.18)	0.04 (0.18)
lymphoma		0.00 (0.06)	0.01 (0.07)
metastatic cancer		0.03 (0.17)	0.02 (0.13)
leukemia		0.01 (0.11)	0.02 (0.14)
immunosuppression		0.05 (0.22)	0.05 (0.22)
cirrhosis		0.05 (0.22)	0.05 (0.22)
diabetes		0.49 (0.50)	0.49 (0.50)
apache score		72.11 (28.93)	71.71 (23.46)
sofa score		8.72 (3.78)	8.61 (2.94)
charlson score		6.14 (3.57)	6.21 (2.48)
hospital mortality (n (%))	Alive	559 (72.79)	605 (78.78)
	Expired	209 (27.21)	163 (21.22)

Table 4. Description of features from matched patients.

3.1.1. Treatment effect

When evaluating on all feature categories, demographics, scoring systems, and comorbidities, the results show that regardless of when looking at the matched patient population or the unmatched population, the OR is always under 1; this indicates that treatment is better than control in terms of patient outcome. *Table 5.* shows the CI, OR, and p-values from both cohorts, showing that the treatment column in the dataset indicating dialysis or no dialysis is statistically significant

Dataset	**Effect of treatment**			
	CI (95%)		**OR**	**p-value**
Entire cohort	0.19385	0.295587	0.239374	p<0.001
Matched patients	0.211568	0.320664	0.260465	p<0.001

Table 5. Effect of treatment evaluated from the matched and unmatched patient cohorts.

3.1.2. Covariate effect

Understanding the treatment effect was one portion of this work, the second was to analyze what other components from the covariates have the most effect on the outcome. The following contains the work done by analyzing the effect of the covariates in each feature category and how their effect compares with that of dialysis.

Demographics

In the demographics category, the weight distribution from the multivariate regression ran on the matched and unmatched patient populations was compared to analyze the differences across covariates on each side. In the original unmatched patients, the top weights were dialysis, gender, and ethnicity. In the matched population, the results showed the same (*Table 6.*).

Demographic	Weights from unmatched patients	Weights from matched patients
Age	0.01799556	0.02159517
Gender	-0.28086929	0.12321948
Height	-0.00932141	-0.00373388
Weight	-0.00387937	-0.00313941
Ethnicity	0.0542727	-0.07996741
Dialysis	0.40528904	0.22596769

Table 6. Effect of covariates and treatment evaluated from the matched and unmatched patient cohorts, looking specifically at the weights of each feature found in the demographics category.

Scoring systems

In the scoring systems category, the weight distribution in both the matched and unmatched populations show that dialysis and SOFA score have the highest weight when evaluating for outcome (*Table 7.*).

Scoring System	Weights from unmatched patients	Weights from matched patients
APACHE	0.02157461	0.0167402
SOFA	0.16526439	0.16659032
Charlson	0.086081	0.04622442
Dialysis	-0.12740236	-0.23920787

Table 7. Effect of covariates and treatment evaluated from the matched and unmatched patient cohorts, looking specifically at the weights of each feature found in the scoring systems category.

Comorbidities

In the comorbidities category, the weight distribution shows to have some differences between the matched and unmatched populations. In the unmatched patients, cirrhosis, metastatic cancer, leukemia, diabetes, lymphoma, and AIDS have more weight than dialysis. In the matched patients, dialysis has the greatest weight followed by cirrhosis and metastatic cancer (*Table 8.*).

Feature	Weights from unmatched patients	Weights from matched patients
AIDS	0.34717237	-0.54781762
Hepatic failure	0.1006441	0.5562587
Lymphoma	0.35783152	0.14800744
Metastatic cancer	0.68180756	0.62214839
Leukemia	0.55446649	0.29735666
Immunosuppression	0.14200942	0.3931692
Cirrhosis	0.92172783	0.72331997
Diabetes	-0.38787572	-0.00712935
Dialysis	0.32026433	0.83334587

Table 8. Effect of covariates and treatment evaluated from the matched and unmatched patient cohorts, looking specifically at the weights of each feature found in the comorbidities category.

All Features

When evaluating on all features, demographics, scoring systems, and comorbidities, the weights are the greatest in comorbidities for both patient populations. In the unmatched patient population, cirrhosis, diabetes, hepatic failure, AIDS, and metastatic cancer have the greatest weights, with the matched patient population having similar results (*Table 9.*).

Feature	Weights from unmatched patients	Weights from matched patients
Age	0.00959445	0.0093803
Gender	-0.14250416	0.02197256
Height	-0.00469702	-0.01193092
Weight	-0.0035002	-0.00191246
Ethnicity	-0.03877222	-0.02556954
APACHE	0.02049662	0.01149608
SOFA	0.16304719	0.16984845
Charlson	0.06217501	0.05433832
AIDS	-0.24593875	-1.0699532
Hepatic failure	-0.40057688	-0.37654518
Lymphoma	0.09818797	0.33277954
Metastatic cancer	0.2224521	-0.32658313
Leukemia	0.18782175	0.07968591
Immunosuppression	0.11376672	-0.01219298
Cirrhosis	0.63928546	0.22029255
Diabetes	-0.43104487	-0.21520131
Dialysis	0.13542967	-0.11161116

Table 9. Effect of covariates and treatment evaluated from the matched and unmatched patient cohorts, looking specifically at the weights of each feature found in all features of the extracted cohort.

Chapter 4

Discussion

4.1. Correlations between features and outcomes

To understand the impact of the features amongst each other and against the outcome, we created a correlation visualization. As seen in *Figure 2.*, the mortality row shows a distinguishable positive correlation between APACHE score and outcome as well as SOFA score and outcome. Other important confounders are age with outcome and Charlson score with outcome. Dialysis on its own does not show to have much correlation with the outcome, and thus additional covariates will be needed to more accurately determine its effect.

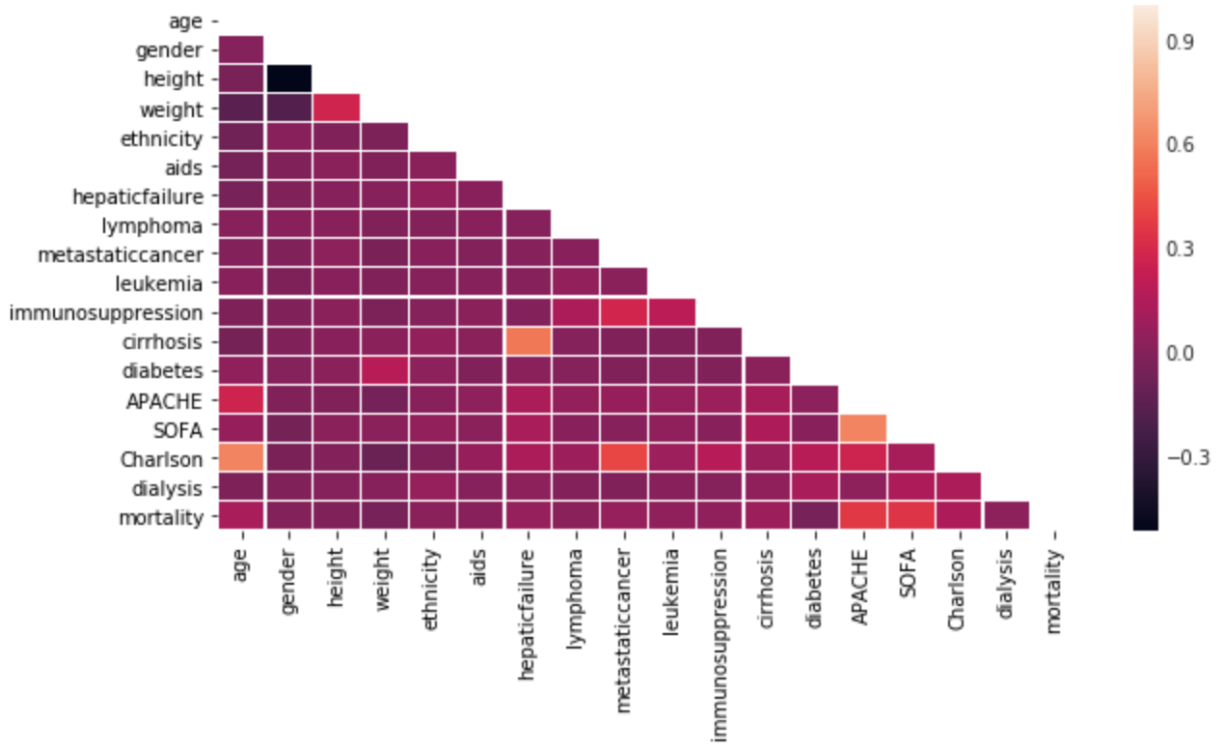

Figure 2. Correlation plot between given features and outcome.

4.2. Regression and propensity score analysis

Propensity score analysis was utilized to match patients from the control group to similar patients in the treatment group. All in all, as *Table 4.* shows, a majority of the covariates matched from both categories, except for the percentage of men to women which increased in the matched treatment group (55.08% vs. 53.78%) and the increase of African American and Other ethnicities in the matched treatment group (25% vs. 15.63% and 5.86% vs. 4.04%, respectively). In terms of the outcome, the likelihood of mortality for the treatment group was 21.22%, 16.54% in the control group, and 27.21% in the matched control group (*Table 10.*). These findings show when looking at patients who have been matched based on similar covariates, that mortality was more

likely when the patient did not receive dialysis versus when the patient did. The odds ratio from the matched patient population was 0.260465 (95% CI = 0.211568 to 0.320664, p<0.001).

Variable	Specific variable	Without dialysis	Without dialysis (matched)	With dialysis
hospital mortality (n (%))	Alive	13026 (83.46)	559 (72.79)	605 (78.78)
	Expired	2582 (16.54)	209 (27.21)	163 (21.22)

Table 10. Hospital mortality from the control, matched control, and treatment groups.

In addition to evaluating the treatment effect, the logistic regression was used to evaluate the effect of the covariates on the outcome. Each feature category provided insight on which weights had more impact in the model: demographics showed gender and ethnicity, scoring systems showed SOFA score, comorbidities showed cirrhosis and metastatic cancer, and all features showed metastatic cancer, cirrhosis, AIDS, and hepatic failure.

4.3. Future work

As this evaluation was done on the eICU CRD database, future work will need to be conducted on the NIS database in order to determine if both datasets can provide the same information or if one will provide more revealing information than the other. Since this work is being done in parallel with Dr. Rush, we will need to collaborate with him to obtain his results on the effects of dialysis. Then we can evaluate the two databases.

In this study, we did not consider past patient conditions or renal complications. This will be an important next step as the past history will provide more insight on the patient's current condition and provide more accurate results concerning the treatment effect. Additionally, in this study we did not account for the initial RRT starting point for each patient. We only generalized

to patients who were currently undergoing RRT and patients who were not. As described in the Related works section, the timing and dosage of RRT can play a large role in determining the outcome of the patient. Thus, we will need to calculate and determine each patient's initial RRT starting point and evaluate patients based on the same start time when modeling for the treatment effect.

Finally, we will extend this study by adding a deep learning component. Essentially, we want to run a neural network that will predict whether each specific patient will benefit from dialysis. So far, the results from the logistic regression and propensity score analysis have given us insight into features and effects of features on the treatment and control groups. The next step will be to build an algorithm that can take these features and the treatment and provide a prediction to each patient's likelihood of mortality.

Chapter 5

Conclusion

The goal of this work was, given the eICU CRD database, to understand the effect of RRT on sepsis patients. This work concludes that RRT does in fact benefit the patient outcome and dialysis is a statistically significant feature within the dataset (OR = 0.260465, 95% CI = 0.211568 to 0.320664, $p<0.001$). RRT, in addition with other covariates, can provide even more accurate results; these include features found within demographics, scoring systems, and comorbidities. The future work of this study includes filtering out patients of interest, including adding patients with past renal complications and calculating each patient's initial RRT starting point. Additional future work includes comparing the results with the administrative database, NIS, in order to understand if both databases can provide similar results. The results from the analysis in both databases will provide the opportunity to better understand how to evaluate outcomes using various hospital health records and how to prioritize important features within a patient's medical records.

Chapter 6

References

[1]: Centers for Disease Control and Prevention. (2017, August 25). *Sepsis Data & Reports*. Retrieved from https://www.cdc.gov/sepsis/datareports/index.html

[2]: Martin, G.S. (2012). Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. *Expert Review of Anti-infective Therapy, 10(6)*, 701-706. doi:10.1586/eri.12.50

[3]: Ronco, C., Ricci, Z., De Backer, D. et al. (2015). Renal replacement therapy in acute kidney injury: controversy and consensus. *Critical Care, 19(1)*, 146. doi:10.1186/s13054-015-0850-8

[4]: Johnson, A.E.W., Pollard, T.J., Raffa, J., Celi, L.A., Badawi, O. & Mark, R. (2017). The eICU Collaborative Research Database, a freely available multi-center database for critical care research. doi: 10.13026/TBC

[5]: HCUP Databases. (2018, February). Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD. Retrieved from www.hcup-us.ahrq.gov/nisoverview.jsp.

[6]: Zimmerman, J.E., Kramer, A.A., McNair, D.S., & Malila, F.M. (2006). Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients*. *Critical Care Medicine, 34(5)*, 1297-1310. doi:10.1097/01.ccm.0000215112.84523.f0

[7]: Bernardina, L.X., Diccini, S., Gonçalves, A. et al. (2008). The clinical outcome of patients with acute renal failure in intensive care unit. *Acta Paulista de Enfermagem, 21*, 174-178. doi:10.1590/S0103-21002008000500007

[8]: Schiffl, H., Lang, S.M., & Fischer, R. (2012). Long-term outcomes of survivors of ICU acute kidney injury requiring renal replacement therapy: a 10-year prospective cohort study. *Clinical Kidney Journal, 5(4)*, 297-302. doi:10.1093/ckj/sfs070

[9]: Ostermann, M., Dickie, H., & Barrett, N.A. (2012). Renal replacement therapy in critically ill patients with acute kidney injury--when to start. *Nephrology Dialysis Transplantation, 27(6)*, 2242-2248. doi:10.1093/ndt/gfr707

[10]: Jones, A.E., Trzeciak, S., & Kline, J.A. (2009). The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Critical Care Medicine, 37(5)*, 1649–1654. doi: 10.1097/CCM.0b013e31819def97

[11]: Charlson, M., Szatrowski, T.P., Peterson, J., & Gold, J. (1994). Validation of a combined comorbidity index. *Journal of Clinical Epidemiology, 47(11)*, 1245-1251. doi: 10.1016/0895-4356(94)90129-5

A. APPENDIX

Variable	Specific variable	Without dialysis	With dialysis	# of null values
n (mean (std) or specified)		16140	791	
age (yrs)		66.08 (16.50)	64.19 (13.76)	0
gender (n (%))	Female	7983 (49.46)	356 (45.01)	0
	Male	8155 (50.53)	435 (54.99)	
	Unknown	2 (0.01)		
height (cm)		168.29 (14.31)	167.88 (15.60)	146
weight (kg)		82.45 (28.68)	82.61 (25.13)	359
ethnicity (n (%))	African American	1467 (9.16)	195 (24.71)	133
	Asian	250 (1.56)	20 (2.53)	
	Caucasian	12800 (79.96)	482 (61.09)	
	Hispanic	639 (3.99)	35 (4.44)	
	Native American	131 (0.82)	11 (1.39)	
	Other/Unknown	722 (4.51)	46 (5.83)	
aids		0.00 (0.05)	0.00 (0.06)	0
hepatic failure		0.02 (0.14)	0.03 (0.18)	0
lymphoma		0.01 (0.09)	0.01 (0.07)	0
metastatic cancer		0.03 (0.18)	0.02 (0.13)	0
leukemia		0.01 (0.12)	0.02 (0.14)	0
immunosuppression		0.06 (0.23)	0.05 (0.22)	0
cirrhosis		0.02 (0.16)	0.05 (0.22)	0
diabetes		0.23 (0.42)	0.49 (0.50)	0

apache score		67.50 (27.31)	71.62 (23.39)	0
sofa score		6.27 (3.51)	8.56 (2.93)	0
charlson score		4.43 (2.90)	6.24 (2.46)	0
hospital mortality	ALIVE	13457 (83.38)	622 (78.63)	0
(n (%))	EXPIRED	2683 (16.62)	169 (21.37)	

Table A. Final cohort of features used from the eICU CRD database (containing null values).

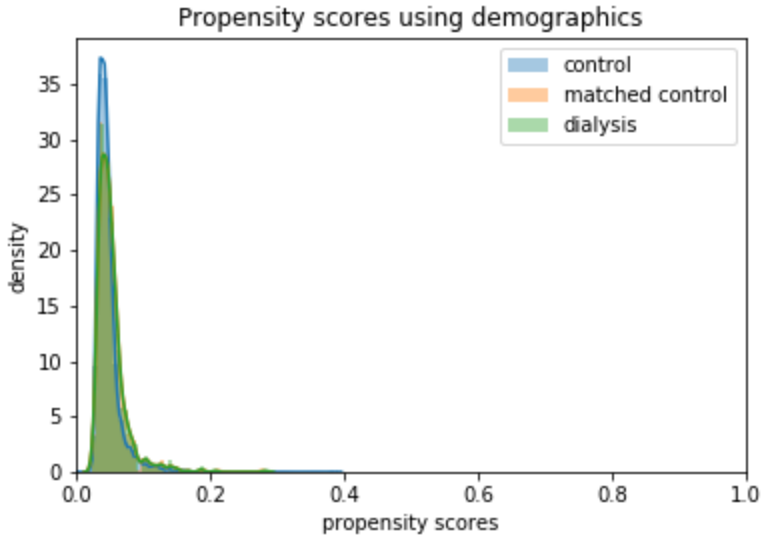

Figure B. Propensity scores for dialysis in the treated, control, and matched control groups, looking at demographics.

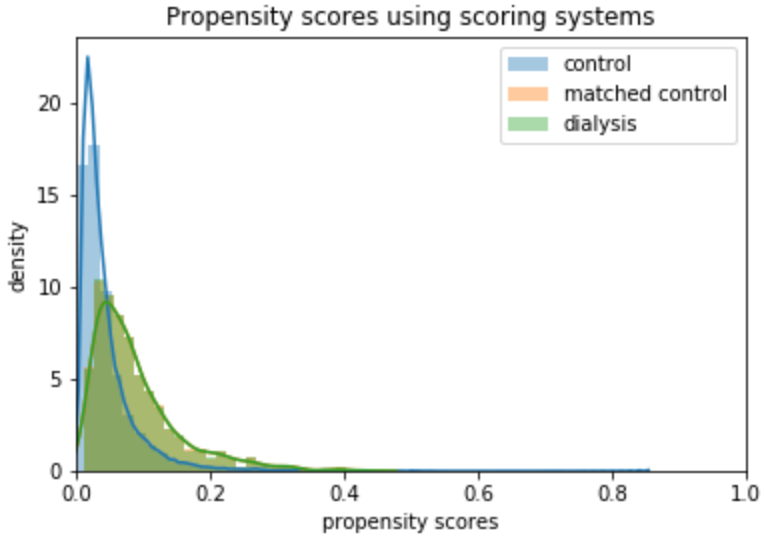

Figure C. Propensity scores for dialysis in the treated, control, and matched control groups, looking at scoring systems.

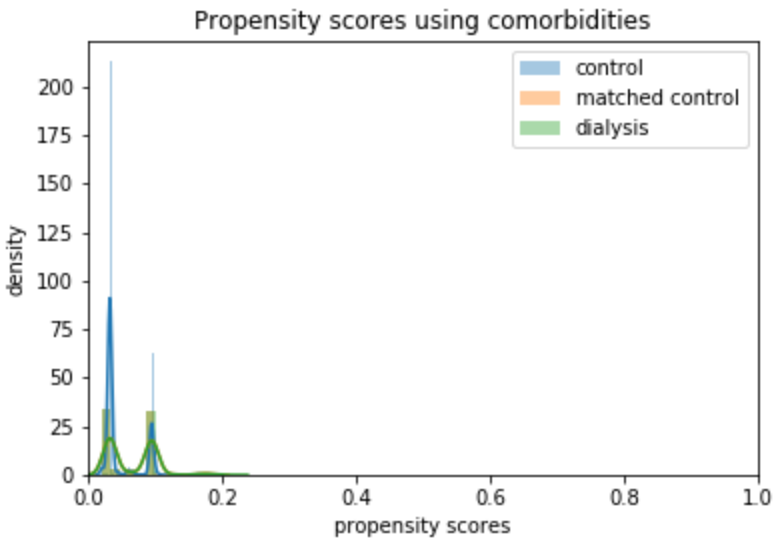

Figure D. Propensity scores for dialysis in the treated, control, and matched control groups, looking at comorbidities.

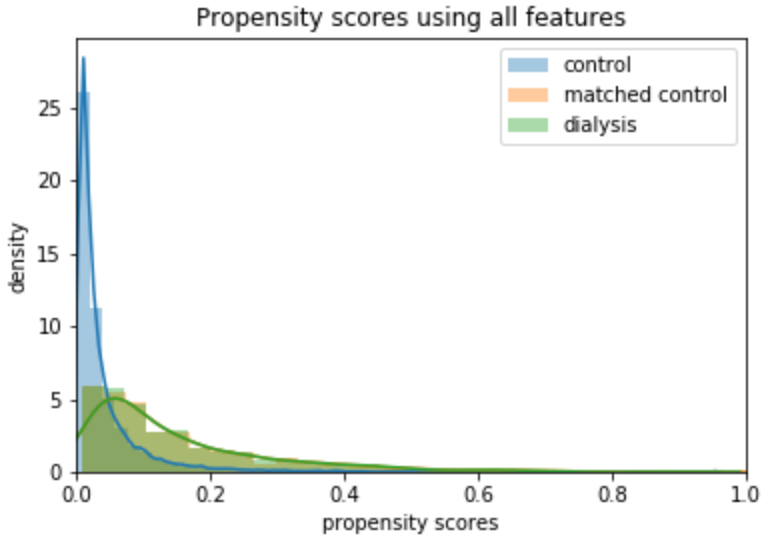

Figure E. Propensity scores for dialysis in the treated, control, and matched control groups, looking at all features.