THE INFLUENCE OF DECEASED KIDNEY DONOR BLOOD UREA NITROGEN (BUN) LEVEL ON GRAFT AND PATIENT SURVIVAL TIME

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ABSTRACT

The Influence of Deceased Kidney Donor Blood Urea Nitrogen (BUN) Level on Graft and Patient Survival Time

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Although the advancement of surgical techniques and immunosuppressive therapy has significantly improved the outcomes of kidney transplantation in patients with end stage renal disease (ESRD), post-transplantation outcomes remain a big challenge. Accordingly, the goal of this dissertation was to determine which variables might have the most critical impact on the graft and patient survival time. One such variable which seemed significant but not well studied was the Blood Urea Nitrogen (BUN) level of the donor. Therefore, using the United Network for Organ Sharing (UNOS) registry database (October 1987 to March 2016), a retrospective (longitudinal) cohort study was setup to examine the relationship between the BUN level of the deceased donor and the survival of the graft and the patient while controlling for certain other variables. The final sample consisted of 168,081 patients in the United States.

Multivariate cox regression analysis revealed that high log BUN level of deceased donor remained an independent predictor of graft loss (hazard ratio [HR], 1.080; 95% hazard ratio confidence limits [CI], 1.032 - 1.131; *P = 0.0009*) and patient death (hazard ratio [HR], 1.063; 95% hazard ratio confidence limits [CI], 1.007 - 1.121; *P = 0.0262*) compared to low log BUN level of deceased donor.

Significant findings from this study indicate that high log BUN level (> 2.79 mg/dl) of deceased donor is independently associated with decreased graft and patient survival time compared to low log BUN level of deceased donor. It is to be noted that White, Black and Hispanic donors races have significant differences at 5 year graft and patient survival time while donors of other races (Asian, American Indian/Alaska native, Native Hawaiian/other Pacific Islander, and multiracial) did not show a statistically significant influence on graft and patient survival due to genetic influences. These results can potentially contribute to a more efficient allocation of resources to donor sources with better outcome prospect.

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CHAPTER I

INTRODUCTION

1.1 Background

Kidneys are paired, bean-shaped organs located in the upper back part of the retroperitoneal cavity on either side of the spine [1]. They are among the most important organs in the human body with critical functions [2]. Each kidney contains one to two million nephrons on average [3]. Nephrons are the main functional and structural units of the kidneys [4]. They clear the blood of non-protein nitrogenous metabolic waste products such as urea, uric acid and creatinine as well as excess water to form urine [2]. Nephrons are the target of most kidney diseases. When nephrons are damaged, the kidneys are unable to function efficiently to remove waste products through the urine. Chronic kidney disease (CKD) affects the nephrons gradually over months to years. Most injuries in CKD are irreversible and may ultimately lead to a decline in the number of nephrons [5 6]. In contrast, acute kidney injury (AKI) damages the nephrons quickly [7], over hours to days [5 8]. AKI is usually reversible in most cases; however, sometimes it is not. Reversibility depends on the cause, severity, associated mortality among hospitalized patients, morbidity, and costs to the health care sectors [5 9 10]. Progression of kidney diseases may lead to end stage renal disease (ESRD) and kidney failure [6 11], and the severity of kidney diseases is a critical factor in the development of this condition [12]. Kidney failure occurs when one's kidney fails to function completely [13]. Once this happens, most patients may require renal replacement therapy (RRT) to slow or stop the progression to ESRD. The

most common forms of renal replacement therapy are dialysis (hemodialysis and peritoneal dialysis) and kidney transplantation [14]. The aims of these therapies are to maintain kidney function and the patient's life [6]. When a patient's kidney function drops to 15% or less, which is measured by an estimated GFR of < 15 mL/min per 1.73m^2, renal replacement therapy is needed [15]. Several studies have shown the survival benefits of kidney transplantation over dialysis among ESRD patients [16]. Kidney transplantation has received vast attention by researchers, and attempts have been made to discover factors affecting the outcomes of the procedure. The success of kidney transplantation outcome is dependent on several risk factors. One of these variables that attracted the attention of researchers is blood urea nitrogen (BUN).

1.2 A statement of the Problem

Accumulating evidence suggests potential adverse outcomes following renal transplantation in patients with high blood urea nitrogen (BUN) levels. However, there is controversial results about the impact of recipient's BUN level on renal transplantation outcomes [17 18]. This creates a gap in the literature that needs to be addressed.

The effect of the BUN level of the recipient recorded after transplantation has been studied in only a limited number of studies. These studies looked at similar variable but not exactly the same as mine. In addition, they are not consistent in their results and they do not indicate a significant influence of BUN level of the recipient on graft outcomes [17 18]. Therefore, my study is different from theirs. As the authors of first study showed that the impact of race and vital status of the donor whether, living or deceased, and they use the recipient's BUN level as an outcome not as indicator, However, they assumed that

lower recipient's BUN level is equivalent to better outcomes [17 18]. The second study did not find any difference in the BUN level of Ig A nephropathy recipients who lost graft vs those who maintained it [17 18]. Therefore, examining BUN levels of recipients and donors in further studies is highly recommended.

Similarly, a few studies have explored the negative effect of increased deceased/living donor serum creatinine (SCr) level as a predictor of graft failure; however, the results have been inconsistent [19 20]. In one study they explored the negative effect of increased deceased/living donor's SCr as a predictor for graft failure, censored for death [20]; however, the results have been inconsistent. In another study by Morgan et al., kidneys from donors were found insignificantly associated with rising and failing serum creatinine, in terms of primary non-function (PNF), delayed graft function (DGF), and early renal allograft survival [19].

There are several studies have investigated the adverse effect of increased recipient SCr as a predictor of graft outcomes [17 18] [21-24]. However, data regarding the effect of donor's BUN level on kidney transplantation outcome is lacking. This may be due to the extreme shortage of deceased donor kidneys over the past 10 years [25].

The fact is, SCr level is more important and much more reliable indicator of renal function than BUN level [26 27]. However, the effect of SCr level on kidney transplantation outcomes has been studied. Therefore, the goal of this study was to examine how BUN level of donor affect the outcomes of kidney after transplantation.

However, the limited knowledge in this area has become the biggest challenge in finding the significant predictors, which influence the outcome of graft and patient survival rate. This study aims to bring out a new dimension in this field of research.

1.3 The Purpose of the Study

The purpose of this study is to test the relationship between the BUN level of the deceased donor and the survival of the graft and the patient while controlling for such variables as donor and recipient's age, gender and ethnicity as well as recipient's hepatitis C virus (HCV) sero-status, hepatitis B virus (HBV) surface antigen, body mass index (BMI) and total serum albumin. Other variables controlled for kidney cold ischemic time (CIT), mode of kidney delivery (on ice or pump), and deceased donor's heart beating status (heart beating or non-heart beating) using the United Network for Organ Sharing (UNOS) dataset.

1.4 Research Goals and Objectives

The overall goals of this research are to:

1. Investigate the relationship between deceased donor BUN levels and renal transplantation outcomes, graft survival time and patient survival time.
2. Clarify whether deceased donor BUN level negatively affects the outcomes of the renal transplant.

The specific objective is to run a statistical analysis on the United Network for Organ Sharing (UNOS) dataset to see if there is a significant relationship between deceased donor's BUN level and patient and graft survival while adjusting for all other confounding variables.

1.5 Significance of the Study

In previous literature, there is controversial over data regarding the association between the recipient's BUN level and the transplantation outcome [17 18]. Therefore, the present study aims to investigate this relationship by examining deceased donor BUN level and transplantation outcomes, graft survival and patient survival, in individuals registered with the United Network for Organ Sharing (UNOS) database.

Understanding the relationship will help us allocate resources to donors with more favorable BUN levels rather than using the resources on donors that are less likely to produce patient and graft survival.

1.6 Research Hypotheses

Based on our knowledge of kidney physiology, higher blood urea nitrogen (BUN) level usually means poor kidney function especially in the absence of prerenal and post renal causes [17 18]. Thus, based on our understanding of kidney function and review of the literature, the following hypotheses were tested in relation to deceased donor BUN levels:

1. Increased deceased donor BUN level is associated with reduced graft survival time.
2. Increased deceased donor BUN level is associated with reduced patient survival time.

CHAPTER II

REVIEW OF THE RELATED LITERATURE

In this chapter, theoretical and empirical literatures relevant to the relationship between several predictors derived from the theoretical and empirical literature and the development of unfavorable post transplantation outcomes among kidney recipients are discussed. The theoretical underpinnings of the etiology of kidney disease development, the treatment options for end stage renal disease (ESRD) as well as the factors that cause unfavorable post transplantation outcomes will be presented. More specifically, the theoretical literature related to the influence of recipient's blood urea nitrogen (BUN) level on transplantation outcomes of kidney and other organs will be reviewed.

Next, the theoretical literature related to secondary predictors, donor and recipient's age, gender and ethnicity as well as recipient's hepatitis C virus (HCV) sero-status, hepatitis B virus (HBV) surface antigen, body mass index (BMI) and total serum albumin. Also, kidney cold ischemic time (CIT), mode of kidney delivery (on ice or pump), and deceased donor's heart beating status (heart beating or non-heart beating) will be covered. The secondary predictors' empirical support and unfavorable post transplantation outcomes will be presented. Finally, gaps in the empirical literature will be recognized, the theoretical rationales for the study questions summarized, and the research hypotheses outlined.

2.1 Renal Anatomy and Physiology: Theories and Empirical Support

Kidneys also are known as *rens*, in Latin [4], they are paired, bean-shaped organs located in upper back part of the abdomen in the cavity called the retroperitoneum on either side of the spine. Kidneys are part of the urinary system [1]. They are one of the most important organs in the human body with crucial physiological functions [2].

2.1.1 Kidney Function

The Greek physician called Galen (AD 129 - 199) was the first to recognize the function of the kidneys is to filter the blood and form the urine. Before this discovery, it was commonly assumed that urine formed in the bladder [28 29]. Nephrons are the main functional and structural units of the kidneys [4]. Each kidney has about a million or two million of nephrons on average [3]. They function to form the urine through 3 processing: filtration, reabsorption, and secretion[4]. They consist of glomerulus and tubules. One of the main functions of the kidney is urine formation. Kidneys filter the blood from non-protein nitrogenous metabolic wastes products such as urea, uric acid and creatinine and excess water [2]. These waste products are freely filtered at the glomerulus while some urea is reabsorbed by tubules. Some creatinine are secreted by the tubules [30]. Unfiltered large molecules, such as protein and blood cells, are absorbed while the filtered fluid, that is composed of waste products and excess fluid, are removed by the kidney out of the body through urine [31]. Also, another function of the kidney is to produce and release hormones that regulate blood pressure, produce red blood cells (RBCs), and control the balance of electrolytes such as sodium and potassium [31 32].

2.1.2 Glomerular Filtration Rate (GFR)

The ability of the kidneys to excrete wastes, such as urea and creatinine are determined by glomerular filtration rate (GFR). A GFR test is used to check how well kidneys are working. Specifically, it estimate how much blood passes through glomeruli each minute [30]. A GFR is broadly known as an indicator of kidney function [33]. Normal glomeruli filter approximately 100 ml of blood to make only 1,500 ml or 1.5 L of urine per day [30].

Kidney function tests are mostly conducted to estimate the glomerular filtration rate (eGFR). The decline in kidney function is characterized by a decline in GFR, which is estimated clinically via eGFR. The eGFR calculations depend on measurements of serum concentration levels such as serum creatinine. Recently, cystatin C also became utilized to measure serum concentration levels through numerous equations [34 35]. Therefore, GFR is a measurement of the function of all of these filtration units (nephrons) in both kidneys [30]. The eGFR is described as the international measurement of kidney function [36]. The measurement of GFR is changeable. It is based on patient's age, gender, race and body mass index (BMI). The normal range of a healthy adult is around 90 - 120 ml/min/1.73 m^2 [36].

A GFR is the amount of the filtered fluid and waste products, so if the filtered fluid is 15 or less means the person has kidney failure. A GFR symptomatic decline is a condition medically called Azotemia or Uremia. Azotemia is characterized by raised serum creatinine (SCr) and blood urea nitrogen (BUN). Insufficiency in kidney function, associated with reduction in urine production, are the fundamental characteristics of kidney failure [37] [38].

2.1.3 Assessment of Kidney Function

The revolutionary discoveries of kidney functions by Galen's and the introduction of urea formation mechanism after 1773 have resulted an obvious development in the evaluation process of kidney function. It took more than a century later to measure the reduction in kidney function by using the increase in urea and creatinine in the blood [28 32]. Kidney function is estimated by using a method called creatinine clearance (CrCl); a 24-hour urine collection. Currently, efforts have been made to study chronic kidney disease (CKD). A clinical practice guideline has been designed in order to evaluate and manage CKD cases. It was provided by a group called KDIGO; kidney disease improving global outcomes. This guideline recommends using prediction equations that are based on serum creatinine to estimate kidney function. These mathematical estimation equations are Cockcroft-Gault (CG), the Modification of Diet in Renal Disease Study Group (MDRD), and the Chronic Kidney Disease Epidemiology Collaboration (CKD - EPI) [33]. Evaluation of renal function by estimating GFR is crucial for patients with chronic kidney disease in order to improve diagnosis and treatment plans [5 39]. The most recommended prediction equation that is recently being used in clinical laboratories to estimate GFR is (CKD - EPI) equation. CKD - EPI equation has advantages over the traditional MDRD. CKD - EPI uses the same four variables that MDRD uses, which include serum creatinine, age, race, and gender. These variables are applied into the following equation: (CKD - EPI $= 141 \times \min (\mathrm{Scr}/k, 1)^{\alpha} \times \max (\mathrm{Scr}/k, 1)^{-1.209} \times 0.993^{\mathrm{age}} \times 1.018$ [if patient is female] or $\times 1.159$ [if patient is black]. CKD - EPI is less bias, more accurate, and precise in contrast to MDRD, particularly if GFR is > 60 mL/min/ 1.73 m^2 [33 40]. A recent retrospective study by Ognibene et al., have evaluated 15,777 adult patients between 2011 and 2013 at

Careggi Hospital laboratory. This study revealed that the (CrCl) equation was not reliable compared to the prediction (CG) equation, particularly with patients with a GFR of 5 ml/min/1.73 m^2/year [33]. CG prediction equation uses four factors: serum creatinine, age, weight and gender. While CG equation is based on the ideal patient's body weight, it is not appropriate in everyday clinical practice. However, the CG equation can be useful with extreme of body weight [5]. Another study was conducted by Kieszek et al that used CG equation to evaluate graft function. It has examined 993 kidney transplant recipients at their transplant center from 1996 to 2010. CG equation was utilized in 7 and 14 days after renal transplantation [41]. In conclusion, despite the disadvantages of some of these methods and equations, they are all still routinely used in many medical laboratories centers to estimate kidney function [33].

2.1.4 Diagnostic Tools for Assessing Kidney Function

Lab tests (blood test, urine test), imaging studies, and kidney biopsy are the most useful diagnostic approaches for assessing kidney failure [42 43]. Blood tests include: measurement of non-protein nitrogenous metabolic waste (e.g. Serum creatinine (SCr), blood urea nitrogen (BUN), and electrolytes (e.g. sodium, potassium, chloride, and bicarbonate)) [44]. Urine tests include urine output evaluation. The decrease or absence of urine production is called oliguria. It is considered as another marker of kidney damage. In addition, urine tests also include color, reaction pH, urine specific gravity, osmolality, and microscopy tests, which determine the presence of cells, casts, crystals, and bacteria. Urine tests also include biochemical examination. The presence of protein in the urine called albuminuria and presence of blood in the urine called hematuria. These two conditions may

be noticed in the urine sample depending on the disease causes. For example, if the disease is caused by diabetes, protein will be noted in the urine test, as well as the presence of sugar, such as glucose [36]. Imaging screening and kidney biopsy detect abnormalities in kidney structure. It includes renal ultrasound that measure kidney size. A small kidney size is an evidence of CKD and indicates hydronephrosis, or kidney swelling, due to the buildup of urine in the kidney [45]. Computed tomography (CT) is another imaging tool, which measures the level and site of renal obstruction [6 46].

2.1.5 Renal Function Biomarkers

2.1.5.1 Definition of the Biomarkers

According to the National Institute of Health (NIH) 2001, a biomarker is defined as an objective measurement that tests the outcome of interventional treatment by representing normal biologic, pathologic processes, or pharmacologic responses to therapy [44].

2.1.5.2 Role of Biomarkers

Biomarkers assist in: 1) providing accurate diagnosis of kidney disease, 2) predicting the illness's progression, and 3) monitoring the response to the therapy, which improves the clinical outcome.

Normal kidney function is measured by renal function biomarkers [42 44]. Renal function biomarkers can be obtained from different human bio-fluids such as urine, tear, saliva and blood samples [47 48]. The biomarkers for glomerular filtration function are

Cystatin C, uric acid, creatinine, and urea and/or blood urea nitrogen (BUN) [42 44 47 49]. Moreover, tubular reabsorption function is associated with biomarkers such as Clusterin, IL-18 and Fetuin [42 44 47].

2.1.5.3 The Significance of Biomarkers: The Main Goal of Early Detection and Treatment

Biomarkers may provide early diagnosis of the disease, which in turn, curtails the disease progression, prevents morbidity such as cardiovascular disease and mortality associated with kidney disease, treats complications, and improves renal therapeutic replacement outcomes [26 50].

2.2 Kidney Diseases

The most common forms are: acute kidney injury (AKI) and chronic kidney disease (CKD) [12].

2.2.1 Definition of Acute Kidney Injury (AKI)

Acute kidney injury (AKI), previously known as acute renal failure (ARF), is a major worldwide health problem that is associated with a patient mortality rate of 1.4 million per year [7 51]. AKI is defined by different classification systems. One of these systems is a guideline provided by Acute Kidney Injury Network (AKIN). Another guideline is based on serum creatinine (SCr) levels or urine output. It was developed by Kidney Disease Improving Global Outcomes (KDIGO).

According to KDIGO guidelines, AKI is defined as an elevation in SCr by 0.3 mg/ dl within 2 days. It is also described as an increase in SCr to 1.5 times baseline within seven days. Moreover, a urine output < 0.5 ml for 6 hours is a sign of AKI [52]. AKI is commonly determined by a severe decline in a patient's GFR [7], and it develops rapidly over a period of hours to days [5 8]. It is characterized by high creatinine, reduced urine production, and accumulated waste products in the blood [8 9]. The incidence of AKI is commonly high among hospitalized [8] and critically ill patients [53]. Approximately, 10% to 20% of adults who are hospitalized in the U.S. are affected by AKI [6]. In a meta-analysis by Susantitaphong et al, 154 studies with 3,585,911 hospitalized patients were evaluated. The study showed that 1 in 5 adults and 1 in 3 children worldwide experienced AKI [54]. AKI is usually reversible in most cases; however, sometimes it is not. Reversibility depends on the cause, severity, associated mortality among hospitalized patients, morbidity in long term outcomes, and costs to the health care sectors [5 9 10]. In addition, even a mild injury may cause long term chronic kidney disease [55].

AKI is a long term risk factor of developing CKD and end stage renal disease (ESRD) [8 40]. In meta-analysis studies that included 13 cohort studies, it was revealed that patients who already had AKI were at an 8.8 fold higher risk of developing CKD while at a 3.1 fold higher risk of developing ESRD [56].

2.2.1.1 Classification of AKI

There are different criteria that have been used to define, classify, and diagnose AKI. In 2004, the Acute Dialysis Quality Initiative (ADQI) group proposed certain criteria for AKI through risk, injury, failure, loss of kidney function, and end-stage kidney disease

(RIFLE). In 2007, the RIFLE criteria were modified by Acute Kidney Injury Network (AKIN) group. Recently, in 2012, these criteria have been revised by KDIGO group in order to enhance the diagnosis and management of AKI. KDIGO criteria are mostly based on changes in SCr concentration level and urine output. However, changes in GFR is not considered within KDIGO criteria, except for patients' < 18-year-old. According to KDIGO criteria, AKI is divided into three stages. Stage 1 b is represented by the increase in SCr concentration levels to ≥ 0.3 mg/dl within 48 hours and urine output ≤ 0.5 ml/ kg/ h for 6 - 12 hours (oliguria). Second, stage 2 occurs when SCr level becomes 2.0 - 2.9 times baseline and urine output ≤ 0.5 ml/ kg/ h for 12 hours. Finally, stage 3 is demonstrated by several criteria. Patients < 18 year are expected to be within stage 3. Moreover, stage 3 includes increases in SCr concentration levels to ≥ 4.0 mg/dl or initiation of renal replacement therapy. Decreased eGFR < 35 ml /min/1.73 m^2, urine output ≤ 0.3 ml/ $kg^{/}$h for 24 hour, or anuria (no urine) for more than 12 hours are considered to be part of stage 3. AKI is detected by the presence of kidney damage markers that include increased SCr concentration level and reduced urine volume [28 57 58]. It is usually classified by urine output per day into - anuric (< 50 mL/day), oliguric (< 500 mL/day), or non-oliguric [8].

2.2.1.2 AKI Pathophysiology

As discussed earlier, possible etiologies or causes of AKI are classified into (1) pre-renal causes, (2) renal or intrinsic causes, and (3) post-renal causes.

Pre-renal causes include hypovolemia (loss of blood volume) [59 60], hypotension (low blood pressure), dehydration, bleeding, sepsis, acute and chronic heart failure, chronic liver disease. Different medications are also considered as pre-renal causes such as

nonsteroidal anti-inflammatory drug (NSAIDs), angiotensin converting enzyme inhibitor (ACEI), Reno vascular disease and CKD. Renal or intrinsic causes include acute tubular necrosis (ATN), sepsis, major surgery, prolonged or total ischemia and exogenous nephrotoxins. Toxins (e.g. NSAIDs, radiological contras, metabolic syndromes (e.g. hypercalcemia and hyperuricemia, autoimmune/inflammatory, glomerulonephritis, and interstitial nephritis)) are also considered causes of intrinsic renal injuries. Lastly, post-renal causes involve acute urinary tract obstruction of bladder tumors, prostatic hypertrophy, and pelvic masses [8 57 60].

2.2.1.3 Risk factors of AKI

AKI risk factors are divided into three major categories: (1) patient factors, (2) operative factors, and (3) pharmacological factors. Patient factors include age above 75 years, male gender, history of CKDs, chronic diseases in heart, lung, and liver, patients with hypertension and diabetes mellitus, or sepsis. Operative factors include blood transfusion, major hemorrhage, surgery (e.g. emergency, cardiac, liver transplantation, vascular and intraperitoneal), and duration of surgery. Finally, pharmacological factors include NSAIDs, antibiotics, and immunosuppressive drugs (e.g. calcineurin inhibitors and radiological contrast) [57 61 62].

2.2.1.4 Clinical Manifestations of AKI

Usually early stages of AKI cause no symptoms [8] until approximately 50% of kidney function has been lost (GFR40 ml/min/1.73 m^2). The only possible initial sign is

oliguria. However, it is not specific or sensitive, as the urine volume may remain normal or increase in some cases [8 37 53].

2.2.1.5 Diagnosis of AKI

Since AKI causes no clinical findings, detection of AKI is based on detailed medical history, physical examination, laboratory measurements including biochemical markers[8]. AKI is detected in hospitalized patients with such conditions as sepsis, major surgery, bleeding, and blood volume loss. Biochemical analysis in AKI shows an increase in BUN and/or SCr concentration levels or dramatic reduction in urine output (oliguria) or both [8 53]. SCr and BUN concentration levels increase when GFR decreases. However, both are neither specific nor sensitive, particularly in early stages of AKI or CKD because their levels start only to increase in the blood when approximately half of the kidney function has been lost. Despite their limitations, they are still clinically used [34 37 53 63].

2.2.1.6 Prevention of AKI

Currently, renal replacement therapy is the best option for treating AKI in life threating situations. Identifying the risk factors for AKI by both health care providers (such as physicians, nurses, trainees) and patients is essential to decrease health care costs and the incidence of AKI. There are a few pharmacological and non- pharmacological interventions that can be used to prevent AKI in high-risk patients. Mostly, the clinical practice relies on non- pharmacological interventions due to less harmful effects compared to pharmacological interventions. These include adequate hydration associated with ICU-free days and treatment of preoperative anemia; preconditioning ischemia. It aims to

protect the organ from prior exposure to an ischemic insult (blood loss/reduction) of the same or another organ. It is delivered by using volatile anesthetics to protect the kidney, hypothermia avoidance, and nephrotoxic drugs (such AS ACE-I, ARBs, NSAIDs). Drug intervention include N-acetyl cysteine (NAC) that prevent AKI. Though, diuretics (loop diuretics) and renal-dose dopamine are ineffective in preventing AKI and may cause additional harm to the organ [64].

2.2.2 Definition of Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is also known as chronic renal failure (CRF) [13]. CKD is a worldwide public health issue in both developed and developing countries [65]. CKD is associated with longer hospital stay and admission, morbidity and mortality due to cardiovascular disease (CVD). In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) defined CKD as a gradual decline in patient's kidney function or GFR and the presence of signs of kidney damage or changes in kidney structure or function for a period of 3 months or longer [5 6 35 40 66].

The disease may develop over a period of months to years in non-hospitalized patients. Most damages in CKD are irreversible and may be characterized by glomerular sclerosis, tubular atrophy, tubulointerstitial fibrosis, and ultimately decline in nephron numbers [5 6 67]. In addition, CKD is a risk factor for developing AKI [8]. Patients who had CKD before developing AKI are at higher risk of developing end stage renal disease (ESRD) [40].

2.2.2.1 Staging of CKD

In 2012, KDIGO guidelines have revised the original classification of CKD published in 2002. There are six categories of CKD classified by KDIGO guidelines based on eGFR to predict CKD outcomes as presented in table 1.

Table 1

Stages of Chronic Kidney Disease

Stage	GFR (ml/min/1.73m^2)	Description
1	≥ 90	Normal or high
2	60 - 89	Mildly decreased
3$_a$	45 - 59	Mildly to moderately decreased
3$_b$	30 - 44	Moderately to severely decreased
4	15 - 29	Severely decreased
5	< 15	Kidney failure

Table 1: Stages of Chronic Kidney Diseases (CKD)

CKD stages 1 and 2 have signs of mild kidney injury but are associated with normal renal function (eGFR > 60 ml/min/1.73m^2). However, they both require more signs of kidney disease such as proteinuria, as a biochemical abnormality or a structural abnormality to confirm the disease. On the other hand, CKD stages 3 to 5 have sign of moderate to severe kidney injury. Kidney injury in stages 1 and 2 are usually asymptomatic and more common in the population than other kidney failure stages. They are detected through routine laboratory testing ordered for investigating other illnesses rather than

chronic kidney disease [13 33 40 68 69]. As a result, only 10% of the non-hospitalized U.S. population are diagnosed with CKD and about 5% of them are diagnosed with stage 3. Moreover, stage 3 is the most common stage in the general population before a subsequent diagnosis is made. Therefore, KDIGO guidelines subdivided CKD stage 3 into 3a and 3b for prognostic reasons. Around 0.1 - 0.2 % of the general population have stage 4 or 5, less common forms of the disease [5 6 13 35 68].

2.2.2.2 CKD Pathophysiology

There are several diseases that may commonly cause CKD. Severe disease may lead to ESRD. Diabetes mellitus (DM) is the most common cause of CKD in many countries such as the United Kingdom, the United State, the Netherland, and Australia, according to a study conducted among these countries. Based on U.S. Renal data system (USRDS) annual data report in 2013, other causes of CKD during the period from 2011 to 2012 include hypertension (high blood pressure), chronic pyelonephritis (PN) renovascular disease (RVD), glomerulonephritis (GN) , and adult polycystic kidney disease (APKD) (a genetic disorder identified by the presence of cysts). DM and hypertension are the most common causes of CKD. In the U.S., GN and APKD are other common causes of CKD among the population [40]. On the same report, CKD incidence rate (per million of population) related to diabetes was 159.2, which accounted for 43.9%. In addition, 102.2 per million population (27.8%) was related to hypertension. Moreover, GN was 23.2 per million populations (6.3%) and APKD was 8 per million population (2.2%). Despite the advancement in diagnostic methods, the unknown causes of CKD among ESRD patients continue to be high in many countries [40].

2.2.2.3 Clinical Manifestations of CKD

The signs and symptoms of kidney failure commonly occur and become more severe when the GFR declines. The severity of the symptoms differs among patients based on the decline in the eGFR levels. However, some patients with the disease have no symptoms despite extreme decline in kidney function. Usually, patients with early stages of CKD are asymptomatic and have few signs. When GFR < 45 ml/min/1.73m^2, some nonspecific symptoms which may appear include fatigue, nocturia, breathlessness, anorexia, and nausea. When GFR falls below 20 ml/min/1.73m^2, specific symptoms occur, but not always exist; including generalized itching called uremic pruritus, restless legs, and insomnia. With the progression of CKD, associated with very low kidney function, and GFR level below 15, severe symptoms present, including hiccups, muscular twitching, fits, drowsiness, coma, and fatigue. Fatigued patients fall asleep during the day, and suffer from vomiting and a uremic smell detected in breath. Other signs of CKD include oedema, pericardial friction rub pericarditis, palpable kidneys, increased bladder dullness and skin changes, such as, pallor due to anemia, pigmentation due to uremia, and scratch marks with bleeding and scarring due itching [68 69].

2.2.2.4 Risk factors of CKD

There are several risk factors related to CKD. Risk factors that may increase the risk of developing CKD, such as age, gender, ethnicity, family history of CKD, genetic factors (polycystic kidney disease, Alport's disease and Fabry's disease), socio-economic status (income, education and environmental factors), metabolic syndrome, high normal urinary albumin excretion, dyslipidemia, nephrotoxins, primary renal disease, urological

disorders (obstruction, recurrent urinary infections), cardiovascular disease, acute kidney injury. Moreover, there are risk factors that increase the risk of CKD progression to ESRD such as African–American race, proteinuria, hypertension, high dietary protein intake, obesity, anemia, dyslipidemia, nephrotoxins, smoking, cardiovascular disease, and acute kidney injury (AKI) [40].

2.2.2.5 Complications Associated with CKD

CKD patients may develop complications such as CVD, anemia, high blood pressure, and ESRD. Each of these complication can be treated by various therapeutic methods [70].

2.2.2.6 Diagnosis of CKD

CKD needs two reading of declined eGFR (< 60 mL/min/1.73m^2) about ≥ 3 months apart to be confirmed. Once the disease is diagnosed, CKD is classified into different stages based on the eGFR and urine albumin to creatinine ratio (UACR) [35 40 69].

2.2.2.7 Prevention of CKD

Understanding the causes and associated risk factors of CKD may assist in early diagnosis and treatment of the disease. In addition, it would subsequently inhibit the progression of ESRD and minimize the number of renal replacement therapy. In turn, this will reduce the cost on healthcare systems [40].

2.3 Incidence and Prevalence of CKD and ESRD in the United States

2.3.1 Incidence and prevalence of CKD in the US

More than 14 % of U.S. adults are estimated to have some level of CKD. The U.S. Renal data system (USRDS) is the largest public health surveillance system of both ESRD and CKD [71] that use data from the National Health and Nutrition Examination Survey (NHANES) during 1988 - 1994, 1999 - 2004 and 2007 - 2012. According to USRDS report at 2015, the prevalence of CKD in the U.S. adult population aged 20 and older remains stable from 2007 - 2012. This result has been observed after many years of increase in 1988 - 1994 to 1999 - 2004 from 2% to 14%. The prevalence of CKD by stages, from 1988 - 2012 among NHANES population, revealed that the prevalence of CKD stage 3 has grown from 4.5% to 6.0% within the period 1988 - 2012. However, the prevalence percentage in both stages 1 and 2 have increased from 1988 - 1994 to 1999 - 2004 and then returned to the early percentage from 1988 to 1994 [72].

2.3.2 Morbidity and Mortality in the Kidney Disease Population

According to USRDS, death rate among dialysis patients have reduced 2 - 3% per year since 2011. The most common causes of death in dialysis patients are cardiovascular complications, such as heart failure and sudden death. However, the mortality relates to acute myocardial infarction diminished among dialysis, transplant, and general populations [71]. The incidence rate of patients who need dialysis increases annually [73 74].

2.3.3 Incidence and Prevalence of ESRD in the US

The occurrence of ESRD has begun to plateau since 2001, decreased each year between 2007 and 2012, and then remained unchanged in 2013. In 2013, about 117,162 patients initiated dialysis therapy for kidney failure with the incidence rate of 363 per million/year [75] in contrast to patients who started dialysis in 2012 [76].

Despite the decrease in the incidence rate of ESRD, the USRDS annual data report of 2015 released that dialysis (hemodialysis and peritoneal dialysis) incidence raised 1.9% from 2012 to 2013, reaching 113,944 new dialysis cases in 2013, which is 24% more than in 2000. Moreover, pre-emptive kidney transplant patients incidence increased 2.6% in 2013, reaching 3,046 pre-emptive transplant kidney, and is now 59.2% higher than in 2000.

In contrast, the prevalence of ESRD in the U.S. population and worldwide continues to rise [77]. The prevalence of ESRD in the U.S. population increases by 21,000 cases annually. Approximately, there were 661,648 prevalent cases of ESRD in 2013, which was 2,034 per million in the U.S. population [75].

According to 2015 USRDS report, the mortality rate continues to decline among ESRD patients on chronic dialysis by 28% or with kidney transplants by 40% since 1996. The decline in mortality among ESRD patients may lead to an increased patient's lifespan, which maximizes patient's prevalent cases [78].

Based on recipient's age and comorbidities, transplantation remains an efficient therapeutic option for ESRD patients due to its advantages that include longer life expectancy of 3 - 15 years compared to dialysis [79].

2.3.4 Incidence Rate of ESRD by Primary Cause

The most common primary causes of renal failure that require transplantation in the U.S. population are DM, hypertension, GN, and cystic kidney disease. ESRD incidence rate (per million per year) relates to DM and hypertension has increased rapidly since 1996 to 2013. However, the incidence related to these two causes has been stable over the past five years. The current incidence rate related to GN has dropped since the 1990s. While new cases related to cystic kidney disease have been stable within the same period. The prevalence related to these primary causes has continued to increase since 1996 [75].

Economically, treatment of ESRD is a major burden to the health care system worldwide [79]. The treatment cost of patients with ESRD within Medicare service in the U.S. has increased by 1.6% from 30.4 billion in 2012 to 30.9 billion in 2013, accounting for about 7.1% of the total Medicare budget. However, the total Medicare cost for general Medicare population has dropped by 0.2% to $437.0 billion in 2013. ESRD spending per patient annually in the U.S. minimized by 0.7% in 2013. Patients with ESRD are representing about 1% of the total U.S. Medicare population. However, they have accounted for about 7.1% of the total Medicare budget. Medicare covers elderly people and extends to people of any age group who require dialysis or transplantation. In 2013, the hemodialysis (HD) treatment cost reached an average of $84,550 billion for total and per patient per year. It remained stable between 2012 and 2013. However, in 2013, the peritoneal dialysis (PD) cost per patient per year was $69,919. Although, the total expenditure continued to increase by 9.2% between 2012 and 2013, the initial cost of kidney transplant surgery was associated with an average of $29,920 billion per patient.

The total per patient per year remained stable between 2012 and 2013 [80] with an expected cost of $25,000 billion per patient per year after surgery [79].

2.3.5 Incidence and Prevalence of ESRD Worldwide

In 2013, among 54 countries, the United States had the highest prevalence rate of treated ESRD at 2,043 per million populations, only after Taiwan and Japan. In addition, the U.S. has also the highest incidence rate of treated ESRD at 363 per million populations only after Mexico (Jalisco) and Taiwan [81].

The percentage of kidney failure in 2013 within the U.S. patients who had DM, a primary cause of ESRD, was 44%. This percentage is the highest in the world only after Malaysia, Singapore and Mexico which account for more than 50% [81].

The incidence rate of ESRD among elderly patients aged ≥ 75 years were high in most countries. The U.S. incidence rate was 1396 per million population. This incidence rate is the highest only after Poland, 3,166 per million population, and Taiwan, 2720 per million population. However, the highest incidence rate among younger patients aged 20 - 44 years old was seen more in the U.S. [81].

2.3.6 Incidence of ESRD by Treatment Option

Internationally, the most common dialysis modality used to treat kidney failure is hemodialysis and represents more than 80% of dialysis treatment in the majority of countries. The most common countries that use the peritoneal dialysis are Hong Kong, Mexico (Jalisco), Iceland, New Zealand, Colombia, and Thailand of 72%, 45%, 34%, 32, 30%, 25%, retrospectively.

According to the USRDS (2015) report, in 2013, the highest rates of kidney transplantation were found in Croatia Mexico (Jalisco), the Netherlands, the United States, and Spain of 59, 58, 56, 56, and 54 per million population, retrospectively. While the highest rates of kidney transplantation in dialysis population were reported in Norway, Estonia, the Netherlands, Scotland and the United Kingdom of 210, 158, 146, 129 and 117 kidney transplants per thousand dialysis patients, retrospectively [81].

The highest constant increase in the kidney transplantation rate (per million population) from 2000 to 2013 were reported in some countries including, Croatia, where the kidney transplantation rate increased from 9 to 59 per million population, the Netherlands from 36 to 56, Korea from 14 to 34, Scotland from 36 to 51, Turkey from 6 to 38 and Uruguay from 17 to 32 [81].

2.4 Treatment Option of ESRD

Kidney diseases is growing problem in the United State today. Progression in kidney diseases may lead to end stage renal disease (ESRD) and kidney failure [11] [6] and the severity of kidney diseases may lead to this condition [12]. Kidney failure also called end stage renal disease (ESRD) which is the last stage of chronic kidney disease or stage 5. Kidney failure occurs when one's kidney is failing to function appropriately [13]. Once this happens, most patients may require renal replacement therapy (RRT) to slow or stop the progression to ESRD [14]. Also the other aim of this therapy is to maintain kidney function and patients' life [6]. The most common forms of renal replacement therapy are 1) dialysis (hemodialysis and peritoneal dialysis) or 2) kidney transplantation. where

dialysis machine and transplanted kidney will take place of the filtering function in the kidney [14].

When patients kidney function drops to 15% or less which is measured by an estimated GFR of < 15 ml/min / 1.73 m^2 of filtered fluid and waste products, means the person has kidney failure and renal replacement therapy is needed [15].

In this study, kidney transplantation as a potential therapeutic choice for patients with ESRD will be studied.

2.4.1 Kidney Transplantation

When the patients are suitable for the surgery, free of co-morbidities and when kidneys are available, the Kidney transplantation is the most effective treatment of choice for the patients of all ages with ESRD.

Kidney transplant_is a treatment procedure that replaces a failed kidney with a healthy one from another person [82]. This healthy kidney can take over the work of two diseased kidneys. However, Kidney transplantation is not a cure [83]. This type of transplant is called allograft or allogeneic transplant or homograft. The first successful human organ transplant was a kidney transplant performed between identical twins in 1954 by a surgical team led by Dr. Joseph E. Murray, of Boston, Massachusetts, in the United States. This procedure was done without using immunosuppressive medication or antirejection drugs [84].

2.4.2 Surgical Approaches to Kidney Transplantation

There are two types of operation in kidney transplantation: 1) heterotopic transplant 2) and orthotopic transplant. In most cases, the healthy transplanted kidney is placed in a different location than the native kidneys, particularly in the front part of the lower recipient's abdomen particularly in the pelvic fossa [85-87] and connects the artery and vein of the donor kidney to the artery and vein of the recipients. Then the recipients' blood flows through the kidney transplanted which forms urine [83]. This type of operation known as heterotopic transplant and it is the most commonly used standard surgical technique in kidney transplantation. It was originally operated by French surgeons team lead by Küss and his colleagues in 1951 and later developed by surgeons' team led by Murray and Harrison in 1954. Deciding which the appropriate side to adjust the transplant is always controversy. Researchers suggest each side of the patient's pelvis (the right pelvic fossa or left pelvic fossa lower site) is suitable. However, the right external iliac vessel is longer compare to the left site, which facilitates connect the blood vessels of recipient to donors in process called the vascular anastomoses. Universally, selecting the right pelvic fossa is preferred to the first transplantation patients while the left side is preferred to the second transplantation. Usually the recipients 'own kidney are remained unless they are causing serious issues to the patient health, for instance, uncontrollable high blood pressure, kidney infection, cancer and enlarge kidney size. Otherwise it assist to decrease the comorbidities [85-87]. Orthotopic transplant can be performed as another alternative and successful procedure for kidney patients when heterotopic inappropriate for them. For example; older patients, patients with comorbidities, patients with vascular disease (e.g. severe atheromatosis and thrombosis of the vena cava), obese patients, and retained iliac

fossae from previous kidney transplant. In this case, Orthotopic transplant is the good choice for these selected patients [85 88].

In this type of transplant, the native diseased kidney is removed and replaced by the new transplanted kidneys from healthy donor in the same anatomic location as the original kidney [86]. Musquera et al., retrospectively analyzed 223 kidney transplant recipients with severe atheromatosis and thrombosis, obesity, retained iliac fossae, who performed orthotopic procedure in two different period of time from April 1978 to January 1987 and from February 1987 to September 2009. Orthotopic procedures performed in 139 patients in the first period and 84 patients in the second period of time. They found that there were no significant differences between urologic and vascular complications in both periods. However, high mortality rate was found in the second period especially among older patients. The graft and patient survival between orthotopic and heterotopic kidney transplants were similar in both period [88].

2.4.3 Advantages of Kidney transplantation vs. Dialysis

Several studies have been shown the survival benefits of kidney transplantation over dialysis among patients with ESRD [16].Improved duration and quality of life, decreased morbidity and mortality, and increased cost effectiveness are also another advantages of kidney transplantation compared to patients on chronic dialysis [88-91].

2.4.4 Type of Kidney Donors

Not all transplanted kidneys are coming from the same vital status. The kidney transplantation sources can be either from living (related-unrelated) or deceased donor who

recently died from brain death or cardiac death [14 92]. Transplantation from live donors continues to be a favorable option for ESRD patients compared to deceased donors. living donor kidney transplantation have better transplantation outcomes following renal transplantation than deceased donor kidneys [77]. Therefore, deceased donor is largely performed [93]. Some deceased donor kidney transplantation can result in better outcomes than some living donor kidneys but the comparison is not on the same scale. Furthermore, deceased donor kidney transplantation usually provides survival benefit compared to chronic dialysis awaiting transplantation [94]. However, the impact of donor types on kidney transplantation outcomes remains controversial [95]. Despite using variety sources of kidney graft either living and/or deceased kidney donors, there is always shortage in donor kidneys availability due to increase in incidence of ESRD in the U.S. population. These pose a greatest challenge facing the field of kidney transplantation today in the U.S and worldwide. As a result, there has been a major increase in the number of patient on kidney transplantation waiting list as well as in the number of patient dying on kidney transplantation waiting list [96]. Moreover, another big challenge in kidney transplantation is immune rejection as a common complication after kidney transplantation [93 97]. With increasing patients with kidney failure and increasing in the number of patients on waiting list, ideal kidney donors cannot be available for each recipient, so donor-expanded criteria are used with better outcomes compare waiting on waiting list. Even though this is valid, transplantation outcomes from optimal donor is better [96].

However, the rate of the deceased donors remained unchanged for the past 10-year's period. To address the shortage of kidney donors availability to cover the patients in need for transplantation, use of marginal donor such as expanded criteria donors [79 91],

UNOS expanded criteria donor (ECD) mostly used to increase the allocation of donor kidneys. UNOS have defined these criteria as using kidneys from donors aged of 50 and older, or kidneys from donors with at least one of these co-morbidities and conditions such as hypertension, or died from stroke or with cerebrovascular disease, and with increase terminal SCr > 1.5 mg/dl [91] With the use of marginal donors, Ojo and colleagues found that increase of life expectancy of 5 years compared to patients with the dialysis [98]. In addition, different policies have been originated to solve this and increase the potential donor pool rather than being on waiting list since many patients die before received the kidneys. For example, in the U.K. study used expanded criteria donors from donors kidney with cancers to kidney recipients [99]. Also, in another study that uses deceased donors who have acute kidney injury (AKI) that defined as serum creatinine >2 mg/dl at the time of transplantation [100].

2.5 Phases of Transplant

2.5.1 Pre-Transplant Period

2.5.1.1 Recipient Evaluation and Selection

This is the time when the patients are on a deceased donor waiting list or before their matching with potential living donors. In this phase, candidates undergo extensive evaluation for overall patient's health and for detection of other health issues or complications that might affect the procedure and outcomes after transplantation [92]. Kidney transplantation is a complex technique that requires development in technical skills

and an expert health care team including transplant surgeon, nephrologist, social worker, dietician, pharmacist, and transplant coordinator [83 92]. Once the evaluation is completed, the kidney transplant team decides whether a kidney transplant is the best choice or not based on patient's health status. These tests include detailed medical history, general physical exam, psychological and physical examination, and routine laboratory and imaging tests, depending on many factors such as patients' age, results of the tests and the primary cause of the disease that led to ESRD. Laboratory test, used for the evaluation of kidney transplant candidates include but not limited to (1) blood typing (2) human leukocyte antigen typing (3) hepatitis B and C serology (4) electrolyte, blood urea nitrogen (BUN) and creatinine. (4) Liver function test. Imaging for evaluation includes but not limited to (1) chest x ray (2) abdominal ultrasound (3) magnetic resonance imaging (MRI) [92].

Kidney function test is one of the routine laboratory tests performed generally to evaluate kidney health status and also to measure kidney failure status in order to monitor the progression of the disease. Kidney function test includes: Hematocrit (HCT), mean cell volume (MVC), blood urea nitrogen (BUN), creatinine, phosphorous, calcium, albumin, sodium, and potassium [70]. In a recent retrospective study, Al-Abdallat and colleges at Royal Medical Services, a total of 263 patients with kidney failure performed kidney function tests for 3 months to examine the efficacy of therapeutic choices for kidney failure patients by changes in the levels of kidney function test. Two readings (means and standard deviations) of the changing of these lab tests were reported. In their result, they found that the variation of the two changing in the level of BUN (1^{st} reading (62 + 19.81) and 2^{nd} reading (69.52 + 30.8), sodium (139.87 + 4.36) (138.85 + 4.29) and potassium (4.62 +

0.83) (4.99 + 0.96)) were significantly significant. While the other test were not significantly significant such as HCT, MVC, creatinine, phosphorous, calcium and albumin [70].

2.5.1.2 Donor Evaluation and Selection

Evaluating and selection potential kidney donor must be accurate by health care team. Accurate evaluation of donor kidney function pre-transplantation is crucial to predict recipient outcomes and to improve kidney transplantation outcomes [101 102].

2.5.1.3 Selection of Living Donors

Selection living donors based on different factors such as blood group, human leukocyte antigen (HLA) typing, anatomy of kidney and general conditions [92] that must have no medical conditions that may increase risk of developing complications following transplantation. Some of these conditions may include infection, malignancy, and kidney diseases that might reduce the recipient kidney function or affect the patient's quality of life [92 101 102].

2.5.1.4 Selection of Deceased Donors

Selection deceased donors depend on 1) blood type, 2) the human leukocyte antigen (HLA) match/ cross-match. This performed by crossed match deceased donor lymph node tissue with recipients serum and lymph node tissue obtained from deceased donor groin area before transplantation [92] 3) kidney condition, anatomy of the vessels and ureter and kidney parenchyma and possible damage. After selection of deceased donor, kidneys

flushed with preservation solution that stored in the cold at 4°C for about 24 hours to the time of the grafted to protect the kidneys from ischemic damages; this time is called cold ischemia time (CIT).

2.5.1.5 Donor Nephrectomy

After living donor kidney selection, kidney can be surgically obtained by open donor nephrectomy, laparoscopic living donor nephrectomy, and laparoscopic hand assistant that each has its advantages and disadvantages [103]. Surgeons prefer left kidney to the right side due to longer renal vein even if there are multiple renal arteries. However, most transplant centers use the right-sided laparoscopic donor nephrectomy if the left sided is not indicated [92 104]. Then the kidney flushed with preservation solution and stored on ice [105].

2.5.1.6 Laboratory and Radiology Evaluation Tests for Assessment Kidney Donor

Potential laboratory tests for live related and unrelated donor include but not limited to (1) blood typing (2) HLA typing (3) hepatitis B and C serology (4) electrolyte, BUN and creatinine. (4) Liver function test. The image evaluation includes but not limited to (1) chest x ray (2) renal ultrasound (3) CT angiography and urography. Living related and unrelated donor remain as important sources of kidney transplantation due to their excellent outcomes and to lessen the shortage of the deceased donor kidney. Deceased donor donation has been expanded, by using expanded Criteria Donor (ECD), but still potential donor should not have medical conditions such as severe chronic high blood pressure,

diabetes, malignant and untreatable infection that many negatively affect transplanted graft function and vascular integrity. Despite the decline of graft and patients survival of using living donor compare to deceased donor, deceased donor donation remains important [92 93].

2.5.2 During transplant surgery period

Because most of the kidneys are from donation from deceased donors, kidneys should be stored in preservation solutions from time of removal until it is transplanted into suitable recipients. Several flush solutions have been used for preserve organs after its removal from the donors. The effective solutions that can be used in kidney preservation include Bretschneider histidine tryptophan ketoglutarate (HTK), University of Wisconsin (UW) solution, and Celsior solution. Because Recipients and donors can be in different location from each other, the preservation time for kidneys can be varies from other organs [105]. Kidney can be transplanted within 24 hours [96] and can be extended to 40 to 50 hours from its removal. However, the earlier getting the transplantation is absolutely the better.

Hypothermic methods are the most preferred method that can be used in kidney preservation. There are two different methods of hypothermic preservation that commonly used in kidney include 1) simple cold storage and 2) continuous hypothermic perfusion machine [105]. The aim of the reservation is to preserve the viability of kidney cells by assist in reduction of cellular activity, delay kidney cell destruction and then diminishes toxic metabolites accumulation to increase graft function after perfusion [91 105]. General anesthesia is performed in this operation and it may take around 2 - 4 hour [85 87].

Minimally invasive kidney transplantation surgery is the one of the modern type for kidney transplantation that may uses robotic surgical system to perform the surgery. [106] laparoscopic renal transplantation is the other successful surgery use but without robotic system assistance. In advantages over open surgery are reduced length of hospital stay, post-surgery pain and recovery time [85].

2.5.3 Post-Transplant Period

This period requires intensive and close monitoring to the kidney-transplanted function and patient's health. After transplant, 1) regular lab tests and other diagnostic tests required to prevent, reduce, or treat the complications that may occur following transplantation. Although the advancement of surgical techniques, tissue typing, and immunosuppressive therapy have significantly improved the outcomes of graft and patriate after kidney transplantation. There are several challenges prior, during and after the surgery that affect the outcomes. However, post-transplantation complications may occur after the surgery and may cause morbidity (cardiovascular events), mortality, and graft failure [85 107]. Many causes may cause decline in the kidney-transplanted function and eventually lead to graft loos or failure. However, the causes may differ over the times after transplantation [14]. The most common factors that might decline renal function in the early period after transplantation and may negatively affect long term graft function and survival include surgical complications that related to kidney recipients such as wound complication, vascular complication, urologic complication, and lymphatic complication [85 107].

Graft failure or graft loss is defined according to many studies as return to chronic dialysis, re-transplant, or death related to renal failure during the follow up period [108 109].

Kidney transplantation recipients are required to have their graft function assessment over time frequently after transplantation to evaluate kidney disease progression and to ensure there are no kidney damages or no risk of kidney function due to one of the causes of the graft failure. Usually there are three biomarkers that are measured constantly over time following transplantation that include BUN, SCr and eGFR [110].

Acute kidney injury (AKI) is one of the primary causes of graft failure among transplanted patients that may cause in the first week post-surgery. This may due to acute tubular necrosis (ATN), hyper acute rejection, a surgical problem and hypovolemia [111]. In a retrospective study conducted by Mehrotra and colleagues, revealed that 11.3% of kidney recipients experienced AKI in the first 3 years following transplantation and concluded that the AKI is an independent risk factors of negative outcome among kidney recipients and associated with 2.74 fold higher risk of graft failure [112]. Recently, in a study conducted by Panek et al. in 326 adult kidney transplant recipients from 2006 to 2014 at their center and found that 21% of patients diagnosed with AKI within the first six months post transplantation. The most cause of AKI due to Calcineurin inhibitors (CNI) toxicity, acute rejection, urinary tract obstruction, and unknown causes. Patients with AKI had reduction of the kidney function at 1 year following transplantation with GFR 5.5 ml/min/1.73 m^2 [55].

Acute rejection, BK virus infection, recurrent focal segmental glomerulosclerosis (FSGS) and ureter obstruction are also the most primary cause of decline graft function during the first 3 months. Chronic rejection, chronic allograft nephropathy, transplant artery stenosis, recurrent or denovo glomerulonephritis and non-adherence to immunosuppression are the most common cause of negative outcome after 3 months following transplantation [14].

Reduced the graft function due to rejection is the most common side effect of the kidney transplantation since some recipients may experience some degree of the rejection as the body may recognized the kidney as foreign object, and immunosuppressive drugs may prevent the rejection. [14]. After transplantation, kidney recipients requires long life medicines called immunosuppressive drugs for the rest of their lives; otherwise the new kidney will be rejected [83 113]. Immunosuppressive drugs are divided into three different categorize that each have special mode of action 1) induction therapy with transplantation to prevent remaking the antibodies that have been removed and improve the immune response suppression in high risk recipients includes antilym-phocyte, 2) maintenance therapy after transplantation used persistently to prevent later acute rejection among high risk patients include sirolimus, tacrolimus, mycophenolate mofetil (MMF), and CsA microemulsion (Neoral), and 3) rescue therapy in case of acute humoral rejection. Current regimes of immunosuppressant showed an excellent short-term patient and graft survival. However, these therapies may increase the risk of developing some form of complications such as: infection (e.g. cytomegalovirus (CMV)), malignancy, and cardiovascular diseases that are associated with morbidity and mortality after transplantation [114 115].To prevent the side effects of current immunosuppressive drugs, there are some of the novel transplant

cellular therapies that recently being used in kidney transplantation include mesenchymal stem cells (MSCs), regulatory myeloid cells, and T regulatory cells [97 116].

Currently, the kidney is the most common solid organ transplanted in the United State based on the Organ Procurement and Transplantation Network (OPTN) data as of April 22, 2016. In 2015, there were about 17,878 out of 30,969 kidney transplanted were performed in U.S. followed by liver, pancreas, kidney-pancreas, heart, lung, heart-lung and intestine which is accounted for 57.7% of all solid transplanted organs [117]. Of these, 12,250 kidney recipients received from deceased donor transplant and 5,628 kidney recipients received from living donor transplants [118].

According to OPTN as of April 22, 2016, there are approximately 100,169 out of 120,928 candidates were on the kidney waiting list were registered on the United Network for Organ Sharing (UNOS) in all states which accounted for 80.9% of all organ types. [119].

In 2009, 3.4 years was the median time for patients in waiting list for first time kidney transplants while approximately a year shorter for repeat kidney transplants. Kidney transplant waiting time continue to increase for deceased kidney donor [90].

The patients in a waiting list may exceed the number of donor kidneys offer, although the number of deceased donors has risen since 2003 to reach 8,021 in 2013 according to the United States Renal Data System (USRDS) annual report 2015 [120].

As discussed above, the development of surgical techniques and immunosuppressive therapy, the outcomes of kidney transplantation among patients with ESRD in all ages have improved significantly [85]. However, any surgical procedure and kidney transplantation as one of them carries risks of complications that may cause

morbidity, mortality, and graft failure. These are some of the unfavorable treatment outcomes affecting patient and graft survival rate. 1) New onset diabetes after kidney transplantation (NODAT) is independently associated with patient and graft survival [121] [122] [123] as well as cardiovascular mortality[124]. 2) Surgical complications that include ureteral obstruction, lymphoceles in postoperative hemorrhage, and renal vein thrombosis may [125] [85 107]. 3) Delayed graft function (DGF) is another common complications after kidney transplantation [126] [123]. 4) Cytomegalovirus (CMV) infection [127]. 5) Acute rejection [123].

Several studies have been addressed the issues of risks of post-operative complications and they tried to minimize them. They studied different risk factors. For example:1) anatomic risk factors (e.g. ratio of donor kidney weight to recipient body weight [128], allograft size to recipient body-weight ratio [129]), 2) biochemical risk factors (e.g. proteinuria of both recipient [18 130] and donor [131]), and 3) clinical risk factors (e.g. hypertension of both recipient [132] [133]and donor [134]).

I am very interested in biochemical risk factors and one of these factors is blood urea nitrogen (BUN) level.

2.5.3.1 Biochemistry and Physiology of Urea

Urea is the major and normal nitrogenous waste product of protein metabolism. Rouelle discovered urea in human urine in 1773 [32]. Liver produces urea from ammonia in the urea cycle, ammonia results from a process called deamination; the breakdown of amino acids. This ammonia is toxic to the body and the body cannot excrete it properly. Urea cycle as a biochemical pathway is converted ammonia into urea. Urea is not toxic

compound and the body through urine can easily excrete it. This conversion known as urea cycle. Urea cycle takes place primarily in the liver, the first two reaction occurs in the mitochondrial matrix of liver cell while the three other reaction occurs in the cytoplasm.1) the combination of the carbon dioxide (CO_2) and ammonia produces carbamoyl phosphate. 2) Formation of carbamoyl phosphate will combine with amino acid called ornithine that lead to form citrulline. 3) The next step, citrulline transported into cytoplasm and it combine with amino acid called aspartate and lead to formation of Arginino-succinate. 4) The next step, arginino-succinase react with arginino-succinate and catalyze it to produce fumarate and arginine. 5) The last step of the urea cycle, arginase react with arginine and break it to produce urea and ornithine. Ornithine is utilized back to the urea cycle [2 135 137]. Where urea is released into bloodstream and then normally removed by kidneys through urine. But when kidneys are damage, urea will accumulate in the blood [138].

2.5.3.2 Clinical Significance of Blood Urea Nitrogen (BUN)

BUN is a biomarker that frequently measured over time for patients who had undergone renal transplantation. As well as to evaluate how well the graft function following renal transplantation [17]. BUN level is the most common test for kidney function. It is a clinical assessment that measures the amount of urea nitrogen in the blood. It aims to evaluate kidney function [135], detect kidney damage, and determine the progression of chronic and/or acute kidney disease [6 49 139].

In some countries for example in the U.K, they measure whole urea to see if the kidneys are working based on the amount of urea and the concentration of urea is reported as millimoles per liter (mmol/l). While in the U.S. and some other countries, they measure

only the BUN (nitrogen part of urea) and the concentration of BUN is reported as milligrams per deciliter (mg/dl) [2 63]. One mg/dl increases in BUN level equals 0.36 mmol/l of urea [2] .The normal range of BUN level in the blood in healthy adults varies between 6 and 20 mg/dl (2.1-7.1 mmol/l). Moreover, in elderly people aged 60 years and older, it is ranged from 8 to 23 mg/dl. Typically, the concentration level of BUN in the blood is slightly lower in children and in pregnancy while slightly higher in male than in female. Patients with renal failure who are not treated with renal replacement therapy tend to have severe high concentration of BUN level with 108 to 135 mg/dl [2]. Elevation of urea level in the blood often indicates decrease in patient's renal function especially in the absence of prerenal and post renal causes [140].

2.5.3.3 The Significance of BUN in Kidney Function

If kidneys are damaged, urea will not be sufficiently filtered by the kidney, leading to an increase in the urea level in the bloodstream [30 138]. The medical condition characterized by elevation in the level of urea and other metabolic waste products level in the blood is called Uremia or Azotemia [37] [38], which means urea in the blood. In 1847, Piorry was the first to use this term to describe a medical condition that associated with kidney failure [63]. It is very essential to know the causes of increased level of BUN and other waste products such as serum creatinine (SCr) levels. It provides better diagnosis and efficient treatment for kidney disease [37].

Changes in urea nitrogen concentrations are associated with decreased urinary output and changes in the nutritional and metabolic states of patient [63]. Elevation of BUN level may be due to prerenal, renal and post renal factors. Prerenal causes include high

protein intake, gastrointestinal bleeding, and low kidney perfusion as a cause of congestive heart failure, and dehydration. Renal causes of BUN elevation are acute or chronic kidney diseases such as acute glomerulonephritis, chronic glomerulonephritis, polycystic kidney disease and other kidney diseases [141]. Lastly, post renal causes include urinary tract obstruction due to malignancy, nephrolithiasis and prostatism [2 63]. Low blood urea nitrogen level may reflect chronic liver disease, malnutrition [5] and repeated peritoneal dialysis [136]. However, urea test is not very sensitive for renal function because it might be affected by renal and non-renal factors. Despite its limitations, the urea test is still clinically used to evaluate renal function [26 27].

2.5.3.4 Analytical Methodology of Urea

Urea nitrogen in the blood can be measured either chemically or enzymatically. Chemical methods are mostly based on Fearon reaction. It occurs when diacetyl reacts with urea to produce measurable yellow diazine compound. The deeper color indicates higher level of the urea nitrogen in the blood. Enzymatic method is more specific and it based on the hydrolytic enzyme, urease that converts urea to ammonia and carbonic acid. The concentration of one of these products is measured to estimate the level of urea nitrogen in the blood [2 142].

2.6 The Impact of Recipient's BUN Level on Outcomes Following Kidney Transplantation and on Various Transplantation Procedure

2.6.1 Kidney Transplantation

Kidney transplantation has received vast attention by researchers, and attempts have been made to discover factors affecting the outcomes of the procedure. One of the variables has attracted the attention of researchers is BUN. There are relatively few studies have claimed that increased recipient BUN concentration level following transplantation is associated with adverse outcomes including poor graft function [17 18]. However, the effects of recipient BUN levels are controversial [17 18].

Regarding the effect of recipients BUN level on transplantation outcomes, in a longitudinal study conducted by Jaffa et al., 103 renal transplant recipient patients were analyzed between 2000-2003 at the Medical University of South Carolina (MUSC). The study aimed to evaluate outcome after kidney transplantation by identifying factors such as age, gender, race, and other factors that affect the rate of change of patients' BUN level. In their method, they measured rate of change of recipient' BUN level among a period of three years after transplantation. Out of 103 patients, 21 patients had missing measurement values of BUN due to graft failure. Patient with graft failure returned to dialysis. In this study, the normal range of BUN level was between (8 mg/100 ml - 25 mg/100 ml). The mean of BUN level was 90 ± 30 mg /ml before transplantation. They found that deceased donors to African-American recipients was associated with an increase in recipients' BUN levels by a total of 1.1 mg/ per 100 ml of blood a month over time following transplantation.

Recipients later experienced poor graft function. However, BUN level was decreased by 0.108 mg/ per 100 ml when recipients were Caucasian. While no effect observed in both Caucasian and African-American recipients when received living donor ($P = 0.075$). Thus, they indicated that donor vital status affected the rate of change for BUN levels then negatively affect the renal outcomes after transplantation. In addition, they found that the rate of change for recipients BUN levels, which influences the success of renal transplantation, had affected by other demographic factors such as gender and race. However, age was not significant. They concluded that, regardless of recipients' ethnicity, BUN levels decrease in both living and deceased kidney donors over time. However, the rate of change of BUN levels decreases fast among recipients of kidneys from living donors in contrast to recipients of kidneys from deceased donors [17].

Opposing to the results of previous study, recently, Guo et al retrospectively analyzed the data at Fuzhou General Hospital in China between 2004 and 2010 to examine the effects of recipient factors on outcomes following renal transplantation. In their study, they aimed to examine the presence of some prognostic factors that might associate with long-term allograft survival in patients with recurrent Immunoglobulin a Nephropathy (IgAN). A total of 197 kidney allograft recipients underwent graft biopsy at their transplantation center. Forty-two kidney recipients were diagnosed with IgAN. Patients were followed up about 2 years after transplantation in every 3 month. In their method, these recipients were divided after transplantation into two groups. Seventeen patients had graft loss during the follow-up period while 25 patients had functional graft. In this study, graft loss was defined as patient return to dialysis or re-transplantation. In their findings, there were no significant differences in BUN level for both groups. The mean of BUN level

among graft loos group was 16.9 ± 9.5 mmol/l while it was 13.5 ± 10.7 mmol/l in functional graft group (*P < 0.081*). Other clinical indicators such as uric acid (UA), hemoglobin, triglycerides (TG) and total cholesterol (CHO) levels resulted insignificant difference in among the study groups. Though, high proteinuria, high serum creatinine, low GFR, low serum total protein and other factors were associated with graft loss [18].

In conclusion, the above two studies are not consistent in their results and they do not indicate a significant influence of BUN level of the recipient on graft outcomes. Therefore, examining BUN levels of recipients and donors in further studies is highly recommended.

The scarcity of studies available on recipient's BUN affecting the outcomes of graft and patient survival have motivated investigations about other predictors that might influence the outcome of kidney transplantation, specifically graft and patient survival. Therefore, this current study hypothesizes that deceased donor BUN level can also be a significant factor that associate with graft and patient survival outcome.

2.6.2 Heart Transplantation

Farrar, DJ conducted a study of 118 patients with preoperative thoratec ventricular assist devices that ultimately received heart transplants. His aim was to investigate the pre-transplant predictors of survival in these patients. By using univariate logistic regression model, he found that blood urea nitrogen (BUN) concentration level and previous operations were significantly associated with lowest survival to transplantation with p-value of 0.02 and 0.05, respectively. While there were not significant differences in age, gender, total bilirubin levels and other predictors. In addition, by using multivariate logistic

regression model he found that blood urea nitrogen (BUN) level was the only independent factor that statistically significant with associated p-value of 0.016 [143].

Above study, indicates a significant impact of BUN level of patients who implanted with ventricular assist device on survival to transplantation and found that recipient BUN level was the preoperative predictor of survival in patients with thoratec ventricular assist devices as a bridge to heart transplantation.

2.6.3 Bone Marrow Transplantation

In a study conducted by Bacigalupo and colleagues, they prospectively analyzed 309 bone marrow recipients who underwent transplantation between 1990 and 1996. In their method, they divided 309 bone marrow transplant recipients into 2 groups according to their BUN levels (The median of BUN is 21 mg/dl). By using univariate analysis model as well as multivariate model after adjusting for certain variables such as; age, calendar year and donor type, they found that, 216 patients with BUN < 21 mg/dl at low risk of transplant-related mortality with 5 years transplant-related mortality of 22% and 93 patients with BUN $\geq$ 21 mg/dl were at high risk of transplant-related mortality with 5 years transplant-related mortality of 44% by using day 7 plus BUN and bilirubin after transplantation. Transplant-related mortality is defined as death due to any transplant related complication. They concluded that, BUN and bilirubin were the predictors in patients who died of transplant-related complications and also in patients who survived the transplant with P value > 0.0001. In addition, these differences increase from day 7 to day 13 after transplantation of P value of 0.00001. By using both BUN and bilirubin levels,

they showed the increase risk of short-term mortality after day 7 following bone marrow transplant [144].

Similarly, Sormani et al. revised the classification of the 305 patients who underwent hemopoietic stem cell transplantation (HSCT) into three groups. Low, intermediate and high-risk patient groups by using day 7 plus blood urea nitrogen (BUN), serum cholinesterase, total protein, and c glutamyl transferase together with donor type and cell dose at transplantation. The proportion of risk of mortality at 6 years for these risk groups was 15%, 40% and 69% respectively. By using multivariate analysis model showed that BUN levels still significant predictor and have strong impact on mortality due to its associated with early renal insufficiency [145].

The above two studies, indicate a significant impact of recipient's BUN level on bone marrow transplantations outcomes. As first study showed that recipient BUN level on day 7 plus after allogeneic bone marrow transplant was the early predictor of mortality and second study also revealed that recipient BUN level on day 7 plus after allogeneic bone marrow transplant remained a very significant predictor of mortality even after revision of the scoring system.

2.7 The Impacts of Prognostic Factors on Outcomes Following Kidney Transplantation

2.7.1 Recipient Age

Recipient and donor age may have an effect on outcomes following kidney transplantation [146]. A study conducted by Matsuoka et al., they retrospectively analyzed

a total of 720 kidney Hispanic and non-Hispanic recipients. Hispanic patients were younger compare to non-Hispanic patients (49.5 years vs. 53.9 years). They found that increased recipient age was associated with lower graft and patient survival time. They conclude that recipient age were an independent risk factor for both graft and patient survival [147].

Similarly, Veroux et al. studied a total of 223 recipients of deceased donor kidney transplants to evaluate the influence of donor and recipient age on outcomes following kidney transplantation. This study performed at the organ transplant unit of the University of Catania between 2002 and 2007. They found that elderly recipients were associated with increased risk of graft failure and patient mortality also elderly recipients has a significant lower graft and recipients' survival rate compared with transplant candidates on the waiting list. They concluded that elderly recipients experience a worse outcomes compared with transplant candidates on the waiting list [146].

On the other hand, with the increase mean age of kidney transplant recipients, Niall et al. studied the outcomes following kidney transplantation in older patient at their center in the United Kingdom from 2001 to 2010. They retrospectively analyzed 762 kidney recipients. Among of these patients, 59 patients were aged $\geq$ 65 years and 703 patients aged > 64 years. They found that there are no differences in delayed graft function (DFG) and graft loss at 1 year among two groups. They concluded that older recipients experienced good outcomes and advance age is not a risk factor for adverse outcomes following kidney transplantation [148].

2.7.2 Donor Age

Niall et al. retrospectively studied the outcomes following kidney transplantation in older patient at their center in the United Kingdom from 2001 to 2010. They found that recipient who received kidney from older donor aged ≥ 65 were more likely to have DGF and Graft loss at 1 year while there was no significant difference in patient survival at 1 year among patient with elderly donor kidney. They concluded that donor age is not associated with worse outcomes following kidney transplantation [148].

However, study conducted by Veroux et al., found that recipient younger and older 65 years of age who received kidney of donor age more than 65 years were at higher risk of graft loss. They concluded that increased donor age is an important adverse predictor of kidney transplantation outcomes [146].

Similarly, another studies also found the older donor age > 50 years were associated with worse graft survival [94] and were more at higher risk of developing DGF at 5 months after living donor kidney transplantation [149].

2.7.3 Recipient Ethnicity

Matsuoka et al., retrospectively analyzed a total of 720 kidney recipients among these patients there were 398 Hispanic and 322 non-Hispanic. The study performed between 2004 and 2013 at their center by using united Network for Organ Sharing (UNOS) database, they found that graft and patient survival rate are similar between Hispanic and non-Hispanic kidney transplant patients. in multivariate analysis results showed that recipient with Hispanic ethnicity is not a risk factor for graft or patient survival rate [147].

However, in a study conducted by Massie et al., they analyzed 106,019 adults first time kidney-only transplant. This study performed between 2005 and 2013 by using the scientific registry of transplant recipients (SRTR) data. They found that African-Americans race were associated with worse graft survival compare to Caucasian, Hispanic and other race groups [94].

Moreover, in another study by Nilakantan and colleges, they retrospectively evaluated 381 kidney transplant recipients at their large transplant center between 1999 and 2013. They found that there was not a significant difference in patient survival at 5 year among the four ethnic groups However, African-Americans has lower graft survival than Caucasians race. They concluded that African-Americans race have worse 5-year graft outcomes following kidney transplantation compared with recipient with Caucasian race [150].

2.7.4 Donor Ethnicity

Callender et al., analyzed 72,495 recipients of deceased and living donor kidney only transplants by using OPTN/UNOS Database between 2001 and 2005.They found that the graft survival rates for Whites and Blacks recipients were negatively affected by donor ethnicity especially kidneys from Black donors. However, kidneys from Black donor only negatively affected patient survival rates when recipients White. In addition, they found that donor kidneys ethnicities are not associated with significantly lower graft and patient survival rate when transplanted into Asian and Latino/Hispanic recipients. They concluded that, Black donor kidneys are independently associated with an increased risk for graft

failure for White and Black recipients while independently associated with an increased risk for mortality for White recipients [151].

In another study by Kristian et al., they analyzed 185 deceased kidney donor recipients. There were 35 African American kidney donors and 150 Caucasian kidney donors. They found that African American donors were a significantly associated with lower graft survival with compare to Caucasian groups. However, there were no differences between two groups in patient survival rate. They concluded that recipients from African American deceased donor had equivalent patient survival rate but lower graft survival when received kidneys from an African American vs. Caucasian donor [152].

2.7.5 Recipient Gender and Donor Gender

Recipient and donor gender impact on outcomes following kidney transplantation is still controversial [153].

Vavallo et al assessed 963 deceased kidney transplant recipients to evaluate the influence of gender disparities between donor and recipient. This study performed between 2000 and 2010 at their center. The patients subdivided into four groups: male donor-to-male recipient, male donor-to-female recipient, female donor-to-female recipient, and female donor-to-male recipient. In the result, they found that there were no statistically significant differences in both graft and patient survival at 1, 3, and 5 years among all groups. They concluded that there was no influence of gender on short- or long-term graft and patient survival rate [153].

On other hand, Chen et al., retrospectively analyzed a total of 766 kidney recipients at their single transplant center to evaluate the impact of gender disparities between donor

and recipient as a risk factor of graft survival after kidney transplantation. In multivariate analysis with step-wise regression showed that male gender were independent prognostic factors for poor graft survival with the risk ratio of 1.3732 compared with graft failure for female patients. They concluded that male gender was an independent risk factor for worse renal transplant survival [154].

Żukowskia et al., analyzed 230 kidney recipients and found there were significant relationships between gender mismatch and early graft loss at 30 days after renal transplantation. Female recipients of male donors showed the lowest graft survival rate compared with all other gender combinations [155]. Also, same findings were found in another study by McGee et al., [156].

Massie et al., also found that, male-to-male donation were associated with better graft survival and concluded that matching donors and recipient will improve renal transplantation outcome [94].

2.7.6 Cold Ischemia Time (CIT)

Several studies in kidney transplantation have been shown that duration of cold ischemia time (CIT) is one of the most independent risk factors that affect transplantation outcomes, graft and recipient survival. Understanding its role in transplantation success can lead to designing strategies to reduce CIT and thus generate better results.

CIT is defined as the time between removes the kidney surgically from the donor for transplantation and grafting into the recipient. The kidney is preserving in a cold solution known as a hypothermic before transplant it into the recipient. The aim of the preservation solutions is to preserve the viability of kidney cells by assist in reduction of

cellular activity and then diminishes toxic metabolites accumulation. However, cell injury cannot completely prevented with CIT [91 157].

Damage to the kidneys during transplantation may occur in this preservation time and longer CIT may cause kidney ischemia reperfusion injuries and negative outcomes on patients and graft survival. However, the effect of CIT on transplantation outcomes is still controversial [115].

Several studies have been shown the negative influence of CIT on outcome post transplantation. In a study conducted by Debout et al., they explained the negative impact of CIT on mid-term renal transplantation outcomes on both graft and patients' survival. Debout et al., studied the association between CIT and graft failure (death-censored) and the patient death. They prospectively analyzed 3,839 first heart-beating deceased donors renal transplant recipients at their center in French between 2000 and 2011. Patients were categorized into four groups according to CIT. 1) CIT from 6–16 hours, 2) 16–24 hours, 3) 24 - 36 hours, and 4) > 36 hour. The mean CIT was 20.6 hours. In their result, they detected that DGF increased with CIT with $p < 0.0001$. 449 of 3,839 patients developed graft loss and 238 patients died with graft function. The risk of developing graft failure and mortality was higher in the first year following transplantation. In unadjusted cox regression model (hazard ratio = 1.018; the 95% confidence interval: 1.007 - 1.030; $P = 0.001$) and in the adjusted multivariate Cox frailty model (hazard ratio = 1.013; the 95% confidence interval: 1.001 - 1.025; $P = 0.035$). These results represented that the risk of graft failure increase with each additional hour of CIT. Also, they analyzed the relationship between the impact of CIT and the patient survival and they found that increase risk of patient's death is associated with increase the each additional hour of CIT [115].

Other researchers reported similar results, van der Vliet and colleagues found that prolonged CIT were associated with reduced graft survival, early graft failure and also increased risk of acute rejection. They analyzed Dutch Organ Transplant Registry data retrospectively of total of 6,322 deceased donor kidney transplant recipients between 1990 and 2007. In multivariate, they observed analysis that length of CIT is independent risk factor for both DGF, Primary non-function (PNF) and acute rejection that lead to reduce on kidney graft survival and graft function. Also in multivariate analysis found that graft failure was associated with prolonged CIT. Graft failure was defined as retranslation. They concluded that prolonged CIT is associated with developing DGF and decreased graft survival while shorter CIT of < 16 and < 20 was associated with better graft survival [158].

Similarly, a cohort study of 829 kidney transplant recipients received kidneys from deceased donor < 50 years old. Hernandez et al. retrospectively analyzed data between 1991 and 2005 at Spain center to estimate the association between the duration of CIT and kidney transplantation outcome. Recipients categorized into two groups according to CIT (< 19 hours' vs < 19 hours). They found that patients with CIT ≥ 19 hours are associated with increase the risk of graft failure (death censored) compare to patients with CIT < 19 hours; 26% and 16.5% retrospectively (*p* value of *0.002*). Multivariate cox regression model revealed that the CIT was found as an independent risk factor of graft failure with 20% increase for every 5 hours of CIT. Similarly, CIT ≥ 19 was associated with increase graft loos compare to CI T < 19 hours [159].

Despite the above studies that indicated an association between CIT and worse renal graft outcomes, some studies have indicated that CIT was not worse significantly associated with graft survival following transplantation.

Recently, in a study conducted by Redfield et al., they analyzed 64 024 adult living-donor kidney transplant recipients between 2000 and 2014 by using UNOS data. Their aim is to examine risk factors for DGF after living-donor kidney transplantation and to investigate the influence of DGF on living-donor graft survival [126]. DGF is define as the kidney dysfunction occur directly after transplantation and defined as need for dialysis within one week after transplantation. DGF is consider as a risk factor of graft failure among deceased donor kidney. It happens due to immunological or ischemia-reperfusion injury [107 160 161]. They were part of the 64,024 recipients, 2,282 experienced DGF, which is accounted for 3.6%. They found several risk factors associated with developing DGF among the recipients. The researchers studied the CIT as a predictor of DGF with other variables such as (Pre-transplantation dialysis, previous kidney transplant, panel reactive antibody (PRA), ABO incompatibility, history of diabetes, recipient BMI, recipient gender, and African American recipient race were independent predictors of DGF after LD kidney transplantation, donor CIT, shipping distance, donor age, donor BMI, and African American donor race, a right donor nephrectomy and open nephrectomy) and found that recipients with longer CIT of 2.6 hours developed DGF compare to recipients with CIT of 2.2 hours who did not develop DGF (*P* value < *0.001*).

A univariate analysis revealed that longer CIT > 12 hours was associated with increased risk of DGF (hazard ratio = 1.447; the 95% confidence interval: .093 - 1.916; *P = 0.010*). Similarly, in multivariate analysis showed significant results (hazard ratio = 1.377; the 95% confidence interval 1.216 - 1.643 *P = 0.037*). DGF was found 2.3 fold higher risk of developing graft failure which is associated with poor graft outcomes. In univariate analysis, CIT showed as a risk factor of graft failure with (hazard ratio = 1.005;

the 95% confidence interval: 1.001 - 1.010; *P <0.001*). On the other hand, the multivariate analysis indicated no significant. They concluded that DGF was the independent risk factor for 5-year graft failure and patient survival and higher among kidney with longer CIT [126].

By using national scientific registry of transplant recipients (SRTR) data, recently, Xia and colleagues analyzed adult first-time kidney transplant patients of paired kidneys from donors with AKI performed from 1998 and 2013 [85]. The CIT difference between kidney transplant patients was ≥ 1, ≥ 5, ≥ 10, and ≥ 15 hours. On multivariate analysis, found that there were no significantly differences between patients with higher CIT to patients with lower CIT in death-censored graft survival when the CIT difference was at least ≥ 1, ≥ 5, ≥ 10, and ≥ 15 hours. Death-censored graft survival was defined as return to dialysis, allograft nephrectomy, or re-transplantation. In addition, patient survival were not statistically significant associated with shorter and longer CIT. also, there were no statistically significant differences in the acute rejection at CIT ≥ 1, 5, 10, or 15 hours [162].

Kayler et al., analyzed cohort of 14,230 expanded criteria donor (ECD) deceased donor only kidney transplant recipient pairs from SRTR performed between, 1995 and 2009. Paired kidney defined as kidneys from one donor but grafted to different patients. Their aim to examine the effect of the CIT on ECD kidney transplant outcomes. Recipients were divided into groups by CIT period. Shorter CIT group as a reference of 7,115 donors, longer CIT group of 7,115 donors, CIT 1 - 3 hour of 2,018 donors, CIT 4 - 9 hour of 3,345 donors, CIT 10 - 14 hour of 938, CIT ≥ 15 hour of 814. Of 14,230 recipients, the median difference in CIT was 5 hours in 7115 donors. They found that patients obtaining the paired donor with longer CIT developed more likely DGF compare to patients with the

shorter CIT (35% vs. 31% with significant ($p < 0.001$). In addition, the DGF increased 42% among recipients with CIT ≥ 15hour when compare the reference group of the lowest CIT (31%). However, they indicated that graft failure was not significantly different between recipient with longer CIT and recipients with lower CIT ($p = 0.47$) or even with 1 - 3 h, 4 - 9 h, 10 - 14 h or ≥ 15 h longer CIT recipient pairs group compare to shorter CIT group. This finding was not different even in multivariable models adjusted for recipient characteristics. They concluded that increasing CIT is an independent risk factor for developing DGF in ECD kidney recipients but graft failure was not statistically difference between 2 groups which is have no impact on graft survival defined as time-to-graft loss or death [85]. This study followed by another one conducted by the same authors in whom the effect of cold ischemia time induced DGF on long-term graft failure. By using the same data performed between 2000 and 2009, they analyzed 18,164 paired kidneys transplant recipients (9082 donors). One recipients develop DGF but not in the other recipients. They included that longer CIT compare to shorter CIT is a risk factor for developing DGF but not associated with reduced long-term graft outcomes of deceased donor kidneys [81].

2.7.7 Recipient Pre-Transplantation body mass index (BMI)

Obesity is a risk factor of developing chronic kidney disease, diabetes, high blood pressure, cancer, and atherosclerotic cardiovascular disease. Obesity is defined as a body mass index (BMI) > 30 kg/m^2 [35 163].

One of the variables that have attracted the attention of researchers is a body mass index or BMI. Accumulating evidence suggests that increased BMI following renal transplantation is associated with adverse outcomes. About 10 kg patient may gain in the

first year following renal transplantation this may be as a risk factor of developing complications include development of metabolic syndrome and new-onset diabetes after transplantation (NODAT) that might reduce graft. Morbid obesity recipients at the time of transplantation should be examined carefully to improve the graft outcomes [164 - 166].

Based on some studies indicating poor outcomes in obese patients mainly because obesity is associated with increased risk of complications post renal transplantation such as cardiovascular disease, diabetes mellitus, and infectious complications such as surgical wound infections. Several transplant centers tend to grafted kidneys to non-obese patients and may reject obese patients with BMI of 30 - 35 kg/m^2 from place them on the waitlist and suggest to lose their weight by for example bariatric surgery to improve the transplantation outcomes after the surgery. However, there were no international criteria for selecting the suitable transplant candidates. Each center creates its own selection guidelines to evaluate the factors of worse outcomes differently. As results, some centers showed better kidney transplantation outcomes with the obese recipients in comparison with other centers [35 167 170].

Understanding the relationship between obesity and transplantation outcomes will help obese patients have a fair access to transplantation, or to make better use of the limited available donor kidneys. The impact of pre-transplant obesity on graft survival had inconsistent results [164 167].

Regarding the adverse effect of pre-transplantation obesity on transplantation outcomes, a recent study by Kieszek et al., retrospectively evaluated 859 adult deceased donor renal transplantation recipients at their single-center in Poland. Patients were divided into 4 groups according to their BMI status into 57 patients with BMI of < 18.5 kg/m^2, 565

patients with BMI 18.6 - 24.9, 198 patients with BMI of 25 - 29.9 kg/m^2, and 39 patients with BMI of > 30 kg/m^2. Recipients observed for one year. They found that recipients with greater BMI were a risk factor of primary graft failure [164].

Similarly, Cannon at el. retrospectively analyzed the UNOS data of 74,983 kidney recipients from 2004 to 2009 to examine the effects of recipient obesity on outcomes following renal transplantation. Patients divided into 4 groups according to their BMI. Non-obese patients with BMI < 30 kg/m^2, class I obese patients with ≥ 30 BMI < 35 kg/m^2, class II obese patients 35 ≤ BMI < 40, and class III obese patients BMI ≥ 40 kg/m^2. Multivariable logistic regression model revealed that obese patients in all weight classes were risk factors of developing DGF. Also, class II and class III obese patients were risk factors of developing non–death-censored graft failure than non-obese patients while Class I obese patient were not. In multivariable analysis, Class II and class III obese patients were not statistically significant in patient survival while class I obese patients were at reduced hazard for death compared with non-obese patients (hazard ration of 0.92 with *P* value of *0.025*) [168].

Moreover, Grosso *et al* retrospectively examined 376 kidney transplant recipients at their single center in Italy between 2000 and 2010 to explore the association between BMI and the patient and graft survival after renal transplantation. In this observational study, patients categorized according into their BMI status into 122 patients with BMI < 25 kg/m^2, 199 patients with BMI of 25 - 30 kg/m^2, and 64 patients with BMI > 30 kg/m^2. Of 376 patients, 312 patients with BMI ≤ 30 kg/m^2 categorized as non-obese patients and 62 patients with BMI > 30 kg/m^2 categorized as morbidly obese patients. They found that obese recipients were at higher risk of developing graft loos compare to non-obese

recipients. Obese recipients had high rate of mortality at 1 and 3-year compare to non-obese. In Kaplan-Meier analysis curve showed that obese recipients had lower graft survival compare to non-obese recipients. In addition, BMI is a risk factor for patient's survival. Univariate analysis model revealed that BMI > 30 kg/m^2 was an independent risk factor for graft loss while in multivariate Cox regression analysis model showed BMI is not continued to be as a predictor of graft loss. BMI > 30 kg/m^2 is an independence risk factor for patient death and statistically significant. They concluded that patient with BMI of > 30 kg/m^2 was an independent risk factor of developing patient death and graft failure [170].

Furthermore several other studies have shown the negative effect of grater pre transplantation BMI on patient and graft survival [171] , [172], and [173].

While several studies reported a significant decrease in graft and patient's survival in obese patients, others found no impact for BMI on transplant outcomes.

In a recent study by Pieloch et al., they retrospectively examine OPTN/UNOS data in 30,132 adults' only kidney transplantation recipients from 2001 to 2006. Patients divided into two groups according to their BMI. Group 1: 24,077 morbidly obese patients with BMI of 35 - 40 kg/m^2. Group 2: 6,055 normal-weight patients with BMI of 18.5 - 24.9 kg/m^2. They defined graft failure as retune to chronic dialysis or death with function graft. By using Kaplan-Meier survival curves, they found that 3-year graft and patient survival were significantly lower among morbidly obese recipients when compare to normal weight recipients. However, multivariate cox proportional hazards regression model for patient and graft survival shows similar findings for morbidly obese recipients and normal weight

recipients. They concluded that BMI of 35 - 40 kg/m^2 is not an independent risk factor of graft failure or recipients mortality [169].

Similarly, Streja and colleagues evaluated 10,090 adult kidney transplantation recipients who were on hemodialysis therapy between 2001 and 2007 using DaVita/SRTR registry data. Patients divided into three groups according to BMI levels into reference BMI group: 22 - 25-kg/m^2, low BMI group: < 20 kg/m^2 and high BMI group ≥ 35 kg/m^2. Patients observed for 6 years. They found that among 10,090 recipients, 727 patients died, 150 died after graft failure, and 759 patients developed graft failures. In the unadjusted model, pre-transplant high BMI was associated with graft failure while in adjustment multivariate model were not revealed this association. They concluded that pre-transplant obesity was not associated with worse post renal transplant outcomes [167].

While the effect of pre-transplant obesity on kidney transplantation outcomes is not clear, the post-transplant obesity is thought to be a risk factor for negative outcomes including graft failure and mortality. Several other factors may confound the relationship between obesity and renal transplantation outcomes that need to be addressed.

2.7.8 Recipient Serum Albumin Level

Serum albumin is another predictive factor that is associated with adverse outcomes following transplantation. Nutritional status is indicated by serum albumin level. A lower serum albumin level or called Hypoalbuminemia is a biomarker of malnutrition, proteinuria, cardiovascular disease and all-cause mortality, comorbidities and inflammation among ESRD patients. Improving pre-transplant patients' nutritional status is very important to predict better long-term renal graft survival. Hypoalbuminemia is also

common after kidney transplantation and may cause permanent graft damage. Serum albumin is a type of blood protein that produced in the liver. The breakdown of the serum usually happens in muscle, liver, and kidneys [107 174 176].

Tutal et al. analyzed retrospectively 189 kidney transplant recipients with at least 12 months of follow-up following transplantation. Recipients classified into three groups according to kidney function or GFR levels. Group 1: patients with normal graft function/ GFR ≥ 90 mL/min, group 2: patients with low renal function/ GFR 89 - 60 mL/min, and group 3: GFR < 60 mL/min. In their results, they found that patients with lower kidney function showed lower serum albumin levels and that associated with loss of graft function among renal transplant recipients [175].

Similarly, Yang et al. retrospectively analyzed 375 kidney transplant recipients at their center from 1991 to 2011. The researchers divided the recipients into four groups according to their pre-transplant serum albumin concentration levels: group 1 (n = 47) had serum albumin < 3.5 g/dl, group 2 (n = 103) had serum albumin varied from 3.5 to 3.9 g/dl, group 3 (n = 117) had between 4.0 and 4.4 g/dl, and group 4 (n = 108) had ≥ 4.5 g/dl. Their purpose was to examine the association between pre-transplant albumin levels and short-term and long-term kidney transplant outcomes as well as DGF, acute rejection episodes, and viral infections among the recipients. The recipient age range from 15 to 66 years old, while the donor age range from 16 to 73 years old. Serum albumin level range from 2.10 g/dl to 5.50 g/dl with mean of 4.05 ± 0.58 g/dl. They found that the rate of the developing acute and chronic rejection, DGF, and infection were similar among the 4 groups.

A multivariate Cox proportional hazards analysis shown that serum albumin levels were an independent risk factors of graft failure. A Cox proportional hazards model

revealed that the relative risk of graft failure among group 4 patients lowest compare to group 1. While the relative risk of graft failure in groups 2 and 3 were similar from that in group1. Kaplan-Meier survival curves revealed that group 1 patients had the worst long-term graft survival compared to the others while group 4 had the best graft survival with a *p* value of *0.039*. They concluded that there is an association between low preoperative serum albumin levels and worse short- and long-term kidney transplant outcomes include graft failure and mortality and other unfavorable post-transplant complications [107].

Similar negative result found also by Molnar et al. study. The researchers analyzed prospectively 8,961 hemodialysis patients who received first kidney transplantation by using huge national data, DaVita. Recipients observed for up to 6 years following transplantation. In their study, they aimed to compare post-transplant outcomes in kidney transplant recipients according to pre-transplantation serum albumin concentration levels. In their method, they divided hemodialysis patients into 5 groups according to their pre-transplant serum albumin levels group1: < 3.77 g/dl as a reference, group 2: 3.77 ≤ 3.97 g/dl, group 3.97 ≤ 4.13 g/dl, group 4.13 ≤ 4.3 g/dl and group ≥ 4.3 g/dl. The results showed that graft failure was found in 785 patients (8.8%), death in 719 patients (8.0%) with *p* value of *< 0.001* for both outcomes. Cox regression analyses model predicted that lower pre-transplant serum albumin levels among hemodialysis patients in the dialysis period was associated with inferior post-transplantation short and long-term complications outcomes include increase risk of graft failure, DGF, all-cause and cardiovascular death [177].

Van Ree et al., prospectively analyzed data of 605 kidney transplant recipients performed from 2001 and 2003. Outcomes observed until August 2007. They conducted the study to examine if the low serum albumin levels as independent risk factor of graft

failure and mortality. Recipients divided into three group according to serum albumin levels into: 1.2 - 3.9 g/dl, 4.0 - 4.1 g/dl, 4.2 - 4.9 g/dl. They found that these factors were independently associated with serum albumin levels. 94 kidney recipients died and 42 patients experienced graft failure (defined as re-transplantation, return to dialysis and censored for death) after about 5.3 years of observation. Cox-regression model revealed that low serum albumin levels was statistically significantly with developing graft failure and mortality when adjusted for both c-reactive protein and urinary protein excretion with hazard ratio of 0.34 and 0.43. They concluded that low serum albumin levels are independent risk factors of developing both graft failure and mortality among kidney transplant recipients and the impact of serum albumin levels on graft failure and mortality are modified by urinary protein excretion [90].

Nevertheless, the association between pre-transplant low serum albumin level and worse renal graft outcomes post transplantation is controversial [107 174 177]. Thus, more data must be compiled to confirm the findings.

2.7.9 Dialysis Modality

Peritoneal dialysis (PD) and hemodialysis (HD) are the most two types of dialysis modality pre-transplantation. Each of these modalities has the advantages and disadvantages. They are both therapeutic techniques of filtering the blood from extra fluid and wastes products. In HD, dialyzer membrane as a filter use with dialysate solution to clean the blood from extra fluid and wastes products while in PD uses peritoneal membrane as a filter and dialysate solution to clean the blood from extra fluid and wastes products [16].

The impact of pre-transplant dialysis modality on post-transplant outcomes is still controversial [178].

Studies investigating the impact of pre-transplant dialysis modality on kidney transplant and recipient survival post transplantation have indicated inconsistent findings.

Although some studies have shown a significant influence of pre-transplant dialysis modality PD or HD and negative outcomes after kidney transplantation. Others have not found this influence.

Kramer et al. analyzed 29,088 living and deceased donor first kidney transplant recipients from 1999 and 2008 by using huge European national data. These adult patients age 20 and older were on dialysis therapy for about 3 months and 10 years. They aimed to observe the association between pre-transplant dialysis modality and recipients and kidney transplant survival after transplantation. In their method, they used multivariable cox regression model to examine the association and the instrumental variable method to reduce confounding variables by indication from unmeasured elements. Of 29,088 patients, 10,135 patients were on PD and 18,953 patients on HD at day 90. In adjusted standard cox regression model, they found that patient and graft survival in patients with pre-transplant PD were better when compared to HD patients. However, in the instrumental variable method, they don't found the association between pre-transplant dialysis modality and outcomes after transplantation [179].

Likewise, Sharma et al. retrospectively analyzed data of 401 adult kidney transplants recipients from 2000 to 2006 at their center. Of 401 recipients, 339 were on HD and 62 were on PD for at least three months before transplantation. The authors were examined the effect of the pre-transplant dialysis modality on patient and graft survival in

African American population which is accounted for 73% of all recipients. In their findings, they exposed that graft and patient survival at 1, 3, and 5 years were similar in both modalities with *P* value of *0.51* and *0.52* retrospectively. Patients with HD were associated with high rate of DGF 38.8% compare to patients with PD 17.7% with significant *P* value of *< 0.005*. There were no statistically significant in graft or patient survival between both groups. In addition, developing vascular thrombosis and infectious complications were similar in both groups. They concluded that patients with PD pre-transplantation have better long-term graft survival in African American population. Moreover, pre transplantation dialysis modality is not a risk factor of long-term graft survival after renal transplantation[180].

Similarly, retrospective study conducted by Mohammadreza et al of 143 patients who underwent first living kidney transplant at single Iranian center from 2002 and 2010. There were 69 patients on PD and 74 patients on HD pre-transplantation. The aim of their study is to examine the impact of dialysis modality on kidney transplantation outcomes including recipients and graft survival, and early and late complication following renal transplantation such as DGF, acute rejection, and post-transplant diabetes. In their results, they found that graft failure developed in 8 recipients in PD treatment group while 16 patients developed graft failure in HD treatment group. Patients with PD have better five-years patients and graft survival compare to HD patients, However, by using log-rank test showed no significant difference between the two groups. Also, the rate post transplantation complications were also not significantly different between PD and HD groups. They concluded that the pre transplantation dialysis modalities are not affect the

recipients and graft survival and the rate of post-transplant complications among patients with living donor kidney transplant [123].

In contrast, Sezer et al. retrospectively analyzed 250 first kidney transplantation performed between 2000 and 2008. Of 250 patients, 70 patients were on PD and 180 patients were on HD. In their results, they found that 16% DGF developed by HD patients while PD patients experienced 16% DGF. The overall graft survival was 82% and 75% at 3 and 5 years, retrospectively. A multivariate analysis indicated that dialysis modality 1.39 fold higher risk developing DGF. With observation period at 3 and 5 years, the rate of graft failure was low among patient with pre-transplantation PD compares to HD patients 14% vs. 20% at 3 years with significant *P* value of $< .05$ and 17% vs. 28% at 5 years with significant *P* value of $< .05$. The authors concluded that pre-renal transplant dialysis modality is associated with a difference influence on kidney transplantation outcomes. Better short and long term outcomes seen among patients treated with PD compare to HD [178].

Similarly, in a large cohort study conducted by Molnar et al. they analyzed DaVita data in 14,508 patients' first kidney transplantation. 12,416 patients were on HD therapy and 2092 patients were on PD. They aimed to study the association between pre-transplant dialysis modality and the patient and graft survival and the post transplantation complication such as DGF. In their findings, cox and logistic regression revealed that patient with pre-transplantation PD therapy had lower mortality rate, lower adjusted all-cause cardiovascular death and lower unadjusted death-censored graft failure and DGF risk when compare to patient with HD therapy. Nevertheless, after additional adjustment for significant factors, pre-transplant PD was not significant risk factors of graft failure and

delayed graft function. They concluded that patients treated with PD had lower recipients mortality but similar graft failure or DGF when compare with patients treated with HD [181].

2.7.10 Recipient Viral Infection

2.7.10.1 Hepatitis C virus (HCV) and Hepatitis B virus (HBV) Infection

Hepatitis virus infections are the common comorbidity among ESRD patients. HCV and HBV infections are the most common among ESRD patients on dialysis sitting and kidney transplant recipients. Kidney transplantation is the most effective treatment option for both hepatitis C virus (HCV) and HBV patients with renal failure over remaining on dialysis. Hepatitis virus infection may affect negatively kidney transplant patients. Moreover, it is as risk factor of graft loss and death in in kidney transplant recipients. However, the influence of these viral infections positively on kidney transplantation outcomes is still controversial. Despite there were some controversies on the influence of HCV on outcomes after renal transplantation, several other studies have confirmed its negative influence on both graft and recipient survival [182 - 186].

2.7.10.2 Hepatitis C Virus (HCV) infection

In a recent study by Xia and his colleagues, they evaluated 3,400 adult paired deceased-donor kidney transplant recipients by using SRTR in U.S. performed from 2000 to 2013. Their goal was to examine the kidney graft outcomes patients with HCV, human immunodeficiency virus (HIV^{+ve}) or viral co-infection. In the pair's donor kidneys, in

which kidneys removed from same donor and grafted to different patients. In their method, the patients divided into two groups according to infected and uninfected with viral infection. One kidney grafted in patients with infection, 1,700 recipients with HCV^{+ve}, and 243 recipients with HIV^{+ve}. The other kidney grafted into patients without infection, 1,700 patients without HCV^{-ve} and 243 patients without HCV^{+ve}. In adjusted multivariable analysis, shown that HCV+ was a risk factor of increase the rate of graft survival and patient survival in comparison with HCV^{-ve}. Also, in multivariable analysis model revealed that HCV^{+ve} was not a risk factor of acute rejection at 1 year following transplantation. They concluded that HCV is a risk factor for worse graft and recipients survival [183].

Similarly, Scott et al. analyzed 7,572 kidney transplant recipients by using Australian and New Zealand Dialysis and Transplant (ANZDATA) registry between 1996 and 2007. They aimed to assess the effect of HCV antibody positive ($HCVAb^{+ve}$) on renal transplant recipient outcomes. Among 7,572 kidney transplant recipients, 140 recipients were $HCVAb^{+ve}$ and 7,432 patients were $HCVAb^{-ve}$. They found that 1686 recipients had graft loss which defined as death with function graft (n = 612) and graft failure (n = 1,074). Graft survival at 5 years was poor among patient with $HCVAb^{+ve}$ compared to uninfected patients. Patients with $HCVAb^{+ve}$ had 1.71 relative risk of graft failure compare to patients with $HCVAb^{+ve}$. The primary causes of graft failure were glomerulonephritis, chronic allograft neuropathy, and death. Hazard ratio was 1.71 and the 95% confidence interval was 1.28 to 2.29. Patient survival was worse in patients with $HCVAb^{+ve}$ at 5 and 10 years after transplantation. 923 patients died at the end of the study period. The primary causes of death were cardiovascular disease, malignancy and hepatic failure causes. They concluded that $HCVAb^{+ve}$ had the worse impact on patient and graft outcome after renal

transplantation [187].

A negative result has found in Morales et al study. Morales and colleagues analyzed data of 4304 renal transplant patients from 1990 to 2002 in Spain. Of these, 587 patients had $HCVAb^{+ve}$. A multivariate Cox models, revealed that the graft survival at 4 years was significantly better in $HCVAb^{-ve}$ patients (94.4%) compared to $HCVAb^{+ve}$ patients (89.5%) with significant *p* value of < 0.005. Patients' survival at 4 years were significantly better among patients with $HCVAb^{-ve}$ (96.6%) in comparison with $HCVAb^{+ve}$ (94.5%) with significant $p < 0.05$. They concluded that compare to negatively HCV, patients with HCV infection had poorer graft and patient survival at 4 years post-transplantation. The most cause of death among HCV patients is cardiovascular, infections and neoplasia. $HCVAb^{+ve}$ was an independent risk factor for the graft loss at 4 year after renal transplantation with significant $p < 0.001$ and odd ratio of 1.702 and CI 95% 1.264 – 2.291. 70 patients with HCV infection have lost their graft. The most common causes of graft loss were biopsy-proven CAN, no biopsy-proven CAN, death with functioning graft, *de novo* glomerulonephritis, late acute rejection, and recurrent original disease. Also, HCV infection was in independent risk factor for mortality, increase rates of proteinuria, lower kidney function, chronic rejection, de novo glomerulonephritis among renal transplant recipients in the short term after transplantation [188].

While several studies have found the negative impact of HCV infection on graft and recipient survival, other studies showed no impact.

For example, Grenha et al., retrospectively analyzed data from 2,284 kidney transplant recipients at their hospital from 1980 to 2012. 62 patients with hepatitis Bs-antigen ($AgHBs^{+}$), 99 patients with anti–hepatitis C virus (HCV^{+}), 14 patients with

AgHBs+ and anti-HCV^{+}, and 2,109 patients were identified with no hepatitis at the time of transplantation. The mean of observation was 7.93 years until graft loss. Graft failure defined as returned to chronic dialysis, recipient's death, or the end of the study. Their aimed was to investigate the impact of these hepatitis virus infections on graft and patient outcomes following renal transplantation. They found that there were no statistical significant among the groups in the rate of graft acute rejection episodes that only induce graft loss and patient survival. However, patients with AgHBs^{+} were associated with statistically significance decrease in graft survival but not in patient survival. They concluded that hepatitis infection is not predictor for kidney transplant survival outcomes. However, AgHBs may decrease the graft survival after transplantation [182].

In addition, Santos et al., retrospectively evaluated 1,224 renal transplant recipients from 1992 to 2006 at their single center. They aimed to examine the effects of pre-transplantation HCV and HBV infections on patient and graft survival. Among these 1,224 patients, there were 28 patients with HBsAg^{+}, 64 patients with anti-HCV, 9 patients with anti-HCV^{+} and HBsAg^{+}, and 1,123 patients without infection anti-HCV^{-} and HBsAg^{-}. In their result, they found that there were no statistical differences in patient and graft survival among the negative and positive groups. The rate of rejection episodes were higher among infected patient (HBV and HCV) than the uninfected patients. However, the association was not statistically significant. The primary cause of death among infected patient with both HBV and HCV infections was liver failure while cardiovascular disease was the major cause of death among patient with HCV infection and negative groups. They concluded that, decreased prevalence of the HCV and HBV infections among kidney transplant recipients over the last 15 years, HCV or HBV infections had no influence on graft and

patient survivals during the observation period [185].

2.7.10.3 Hepatitis B Virus (HBV) Infection

Reddy et al., analyzed data of 75,681 adult primary renal transplant recipients between 2001 and 2007 by using OPTN/UNOS database. They aimed to evaluate the pre-transplantation HBV infection on the patients and graft survival after kidney transplantation. Patients divided into two groups according to HBV infections. There were 1,346 patients with $HBsAg^{+}$ and 74,335 patients with $HBsAg^{-}$. In their results, they found that there were no statistically significant differences between the two groups in patients and graft survival at 5 years. The rate of hepatic failure was higher among recipients with HBV infection (1.3%) compare to HBV non-infected recipients (0.2%); ($P < 0.001$). HBV^{+} is a higher risk of developing hepatic failure in both deceased and living donors compare to HBV^{-}. They concluded that $HBsAg^{+}$ were not as a risk factor for graft failure and patients death; however, patient with $HBsAg^{+}$ were at higher risk of developing liver failure after renal post transplantation [189].

In a recent study by Tsai and colleagues, they analyzed 3,825 Asian kidney transplant recipients. The researchers performed a nationwide longitudinal study in Taiwan between 1997 and 2006. Asian heritage more likely to infected with HBV infection than other ethnicity. Patients divided onto 2 groups. There were 297 patients had HBV infection and 3,528 patients without HBV infection. These recipients observed for a mean of 7.4 years. They found that there were significant differences between the two groups in patient and graft survival at 5 years before and after the ears of anti-HBV drugs (1997 to 2001) and (2002 to 2006). They concluded that HBV^{+} was not negative predictors of kidney

transplantation outcomes. Recipients with HBV infection had similar patient and graft survival rate compare to recipients without HBV infection [190].

Similarly, Santos et al. found HBV infections had no influence on graft and patient survivals during the observation period [185].

Others found association between the pre-transplantation HBV infections and inferior renal transplantation.

Kieszek et al., found that HBV infection is significantly affect kidney graft function. Patients with positive HBV have 1.58 higher risk of developing DGF episode [41].

Similarly, Grenha et al., found that patients with $AgHBs^{+}$ were statistically significance associated with decrease graft survival but not patient survival. However, $AgHBs^{+}$ may decrease the graft survival outcome [182].

2.7.11 Mode of Kidney Delivery on Ice or Pump

Hypothermic storage method is the preferred method of deceased kidney donor allograft. The most common modalities to preserve kidney grafts after retrieval from a donor are 1) static cold storage (CS) on ice 2) hypothermic machine perfusion (MP). Cold storage method is flushing blood out of the kidneys via renal artery and replaces it with chilled preservation solution. Then, the kidney keeps in a bag of preservation solution at 0 - 4 °C and stays on melted ice. On other hand, the kidney in a hypothermic machine perfusion device is stored in a bath of preservation fluid surrounded by an ice. The preservation fluid is withdrawn and pumped through the renal artery [191]. Currently, most deceased kidneys are preserved by CS. However, many studies showed the advantages of

MP over CS particularly in high risk kidney donors such as expanded criteria donor (ECD) and a donor after cardiac death (DCD) to reduce the injury that caused by cold ischemia [192]. The preferred preservation techniques used on graft survival and patient survival remain inconsistent [191]. In comparison to CS, several studies have shown the significant result of using MP with lower risks of delayed graft function (DGF) which is then associated with higher rate of graft dysfunction, acute rejection and lower patient survival time.

In a retrospective study conducted by Gill et al., they examined 94,709 deceased donor kidney transplants in the U.S. between 2000 and 2011 by using the SRTR data. They found that regardless of donor type, standard criteria donors after brain death (SCD), ECD, DCD and cold ischemic time, MP was associated with reduction of risk of DGF. They concluded that reduction of the DGF among patient was associated with utilizing MP in all deceased donor transplants [193].

In a retrospective study conducted by Cannon and his colleagues, they analyzed UNOS data from 2005 to 2011. Their aim was to estimate the influence of MP in comparison to CS on early kidney transplant function in term of DGF. In their method, they analyzed two groups; MP and CS kidneys propensity matched cohort and paired kidney analysis cohort from the same donor in which one kidney placed on MP while the other on CS. In their result, they found that in the overall cohort, the patient who received kidney who underwent MP and CS pre-transplantation were not associated with significantly lower rates of DGF (25.7% vs 25.0%; $p = 0.082$). In addition, they found that in the propensity matched and the paired kidney analysis, kidneys undergoing MP was associated with significantly lower rates of DGF compared with kidneys undergoing CS

(*P< 0.001*). MP and CS group in the propensity matched analysis and in the paired kidney analysis were not associated with significantly graft failure. They concluded that MP is associated with significantly decreased rates of DGF despite of longer cold ischemic time which is in nature, higher among kidneys stored in MP [194].

However, other studies showed no difference significant in kidney transplantation outcomes between kidneys preserved in MP and kidneys preserved in CS.

Jochman et al., analyzed 164 recipients of DCD kidney donors within Euro transplant trial. They revealed that no significant differences at 1 - year patient and graft survival in MP and CS groups. although MP was associated with a reduced risk of DGF and better early graft function up to 1 month after transplantation in comparison with CS [195].

Similarly, in a meta-analysis conducted by Deng et al., they showed that although the incidence rate of DGF were lower among recipients with a DCD kidney preserved by MP compared to a DCD kidney preserved by CS, there were no significant differences after 1 year in both groups in incidence of primary non-function, graft survival or patient survival [196].

2.7.12 Deceased Donor's Heart Beating Status (Heart Beating or non-Heart Beating)

Living donors and heart beating deceased donors, brain dead (BD) donors, are the most common source of organs for transplantation in most countries. To increase the heart beating deceased-donor kidney transplants pool due to the chronic organ shortage worldwide, marginal, extended criteria donor (ECD), and non–heart-beating, donation

donor (NHB), cardiac dead (CD) donors, are broadly used [197] [198]. The Organ Procurement and Transplantation Network (OPTN) have defined ECD kidneys as donors either from a brain-dead donor age 60 years and older, or donors 50 – 59 years of age with at least two of these following comorbidities (1) history of hypertension (2) cerebrovascular cause of brain death or (3) serum creatinine level > 1.5 mg/dl (133 mmol/l). Any deceased kidney donors not meeting these criteria was defined as standard criteria deceased donor (SCD) [199] [200].

Recipient with CD grafts are at higher risk of developing DGF or primary non-function, as well as worse survival and kidney function following kidney transplantation due to ischemic damage that are related to CD kidneys. Most studies of CD kidney transplantation confirm adverse short term and long term outcomes , However, recipients of CD kidneys generally have improved survival compared with wait-listed dialysis patients [197] and also have been shown good results with long-term outcomes comparable with BD kidneys [201].

In regards to comparable outcomes to those with BD kidneys, Barlow and colleagues retrospectively analyzed 276 non-heart-beating donor (NHBD) and heart beating donor (HBD) renal transplants between 1992 and 2002 at their center in the U.K. The aim of the study was to evaluate the long-term graft survival and function of renal transplants from NHBD compared with HBD renal transplants groups with about 5 - 15 year follow-up. In their method, they compared 112 NHBD renal transplants with 164 HBD renal transplants and found no difference in primary non-function while found difference in delayed graft function rates, serum creatinine levels, and graft and patient survival times. They concluded that the long-term survival from NHBD was similar to those from HBD.

However, there was a worse survival and graft function from 10 years post-transplantation [202]. Similarly, Thomas et al. analyzed data from 2002 to 2007 at their center in the U.K and found the difference in short-term outcomes in term of primary non-function (PNF) and delayed graft function (DGF) while the long-term survival of patient from NHBD was similar to those from HBD [203].

Also in another retrospective study by Singh et al., they analyzed 578 adult kidney transplants recipients. Of these patients, 70 from DCD and 508 from DBD kidney donors and they followed up for 36 months. They found differences in DGF and acute rejection groups while no differences were seen in patient and graft survival rates among two groups [204].

CHAPTER III

METHODOLOGY

This study used a retrospective design to examine the association of deceased donor blood urea nitrogen (BUN) level and two kidney transplantation outcomes including graft survival time and patient survival time in a huge sample of patients of the United Network for Organ Sharing (UNOS) database. This chapter presents the study design including the data source, data elements, exposures, outcomes of interest, data organization and cleaning, and statistical analysis for this work.

3.1 Research Design

This study is a secondary analysis of retrospective (longitudinal) cohort studies conducted to explore the associated risk factor of deceased donor blood urea nitrogen (BUN) level on kidney transplantation outcomes of graft survival time and patient survival time. A retrospective cohort study was conducted for adults aged 18 years and older who underwent renal transplantation between October 1987 and March 2016, and were registered in the United Network for Organ Sharing (UNOS) database. The study population consisted of 168,081 adult primary kidneys only transplantation from deceased kidney donors.

3.2 Data Source

Data from the United Network for Organ Sharing (UNOS)/ Standard Transplant Analysis and Research Files (STAR) with corresponding follow-up were obtained for research purposes.

Data from the UNOS database was obtained, which included the information about the donors (both living and deceased) and recipients of renal transplantations reported to the Organ Procurement and Transplantation Network (OPTN) since October 1st, 1987. Each record in the database corresponds to one transplant or waitlist registration case and includes the most recent data such as the patient and graft survival. Each follow up is documented through one record, thus creating multiple records per transplant. To protect patient and center privacy, only patient ID number is used, while any identifier information about patient or center is excluded. The dataset used for the current study collected between October 1987 and March 2016.

3.3 Data Elements

The primary independent variable was the deceased donor blood urea nitrogen (BUN) level. Adjustment covariates included donor and recipient's age, gender and ethnicity as well as recipient's hepatitis C virus (HCV) sero-status, hepatitis B virus (HBV) surface antigen, body mass index (BMI) and total serum albumin. Other variables controlled for include kidney cold ischemic time (CIT), mode of kidney delivery (on ice or pump), and deceased donor's heart beating status (heart beating or non-heart beating). There were 13 different patient subgroups identified and used to compare outcomes in recipients receiving deceased donor BUN. Subgroups were selected based on common

characteristics known to affect outcomes in kidney transplantation.

3.4 Exposure and Outcomes of Interest

Survival Outcomes Definition

Our primary outcomes were: 1) graft survival time and 2) patient survival time. GSTATUS_KI is one of the variable that used to identify graft status for kidneys in the STAR file, 0 = No, 1 = Yes. Graft failure in the GSTATUS_KI variable is defined as (a) patient death, or (b) transplant center reported the graft as having failed (this could be for recipients who had not yet returned to dialysis but had sufficiently low GFR to require relisting), or (c) center reported the patient as having returned to dialysis but did not report the graft as having been failed.

The graft survival time in the variable GTIME_KI is tied to GSTATUS_KI. Graft survival was defined based on the time in days from transplantation to the first most recent reported event between death, graft failure, dialysis, or most recent follow-up date for recipients with still-functioning grafts.

PSTATUS is one of the variable that used to identify patient mortality for kidneys in the STAR file and is defined as (1 = Dead, 0 = Alive).

The patient survival time in the variable PTIME is tied to PSTATUS. Patient survival was defined based on the follow-up time in days from transplantation to patient death or patient last follow-up.

3.5 Data Organization and Cleaning

Data for this study were obtained from the UNOS/ STAR files from October 1987 to March 2016. The study population consisted of all adult patients age 18 years and older who underwent primary kidney only transplantation from deceased kidney donors. Patients' previous kidney transplantations and multi-organ transplantation were excluded.

According to the UNOS/STAR file, the results of deceased donor BUN level tests performed nearest to the time of organ recovery.

Data of deceased donor BUN level is not normally distributed. It ranges from 0.10 to 250.00 mg/dl. Log of deceased donor BUN level was used a preprocessing step to make data normally distributed. The log of deceased BUN then used to create categories. It ranges from -2.30 mg/dl to 5.52 mg/dl. It divided into 3 categories: high-level > 2.79 mg/dl, low-level < 1.93 mg/dl, and medium level 1.93 - 2.79 mg/dl.

Log deceased donor BUN level that categorized into high, medium, low was used for entire analysis.

Seven new independent variables (confounding variables) were also created from continues variables of recipient/donor age, recipient/donor ethnicity, recipient body mass index (BMI), recipient serum albumin, and kidney cold ischemia time (CIT).

Recipient age ranged from 18 to 96 years old. This age group was divided into 18 - 29 years, 30 - 39 years, 40 - 49 years, 50 - 59 years, 60 - 69 years, and ≥ 70 years. Donor age ranged from 0.0 to 88 years old. This age group was categorized into 0.0 - 17 years, 18 - 29 years, 30 - 39 years, 40 - 49 years, 50 - 59 years, 60 - 69 years, and ≥ 70 years. Recipient and donor ethnicity group were divided into White, Black, Hispanic, and other races (Asian, American Indian/Alaska native, Native Hawaiian/other Pacific Islander, and

multiracial). Recipients BMI ranged from 15.0 to 74.2 kg/m^2. Obesity is categorized based on recipient BMI into: non-obesity; BMI < 30 kg/m^2, obesity class I; BMI 30 - 35 kg/m^2, obesity class II; BMI 35 - 40 kg/m^2, and obesity class III; BMI > 40 kg/m^2. Recipients' total serum albumin ranged from 0.50 to 9.90 g/dl and categorized into < 3.5 g/dl, 3.5 to 3.99 g/dl, 4.0 - 5.49 g/dl, and ≥ 5.5 g/dl. Kidney cold ischemic time ranged from 0.00 to 187.00 hours and the times were divided into < 16 hour, 16 - 24 hours, 24 - 36 hours, and > 36 hours.

Graft and patient survival time were converted from days into years by subdivided them by 365.25.

After all exclusions, 168,081 recipients receiving kidney allograft were included in the primary analysis.

3.6 Statistical Analysis

Descriptive statistics of categorical variables will be reported as percentages using PROC FREQ. Similarly, descriptive statistics of continuous variables will be reported as mean and standard deviation (SD) using PROC UNIVARIATE. A chi-square (X^2) test was used to examine whether there is a significant association between the expected and the observed categorical variables in one or more categories. Analysis of variance (ANOVA) was used to assess whether there are any statistically significant differences between the means of three or more independent groups. Two-sample student's t test (t-test) was used to determine whether there are any statistically significant differences between the means of two independent groups. Two analytic approaches for survival data (time to event) were performed: Kaplan-Meier estimator (product limit estimator) using PROC LIFETEST and

the cox proportional hazards model using PROC PHREG. Kaplan-Meier survival analysis was used to compare the survival between three recipient groups in the length of time after kidney transplantation until first occurrence of the primary outcome. The Cox regression model was used to detect when recipients were most likely to experience death and graft failure after kidney transplantation. In addition, to measure the effect (hazard ratio) of deceased donor BUN level on the graft and patient survival time after adjusting for the effect of other possibly influential variables.

The final analytic sample consisted of 168,081 adult primary kidneys only transplantation from deceased kidney donors in the U.S.

If the data had non-normal distribution, a preprocessing step was performed (log). All statistical analyses were performed using the SAS software, (SAS® University Edition), and all tests were two tailed and a value of $P < 0.05$ was considered statistically significant.

CHAPTER IV

RESULTS

The purpose of this study is to address the important gap in both theoretical and empirical literature by determining the relationship between the blood urea nitrogen (BUN) level of the deceased donor and the survival of the graft and the patient while controlling for such variables as: donor and recipient's age, gender and ethnicity as well as recipient's hepatitis C virus (HCV) sero-status, hepatitis B virus (HBV) surface antigen, body mass index (BMI) and total serum albumin. Other variables controlled for include kidney cold ischemic time (CIT), mode of kidney delivery (on ice or pump), and deceased donor's heart beating status (heart beating or non-heart beating). Unfavorable transplant outcomes were defined as worse graft and patient survival times. The data was obtained from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) files. The original data observations were 835,887. The final analytic sample consisted of 168,081 adult primary kidney-only transplantation from deceased kidney donors. Analysis of the data from this study will be presented in this chapter.

4.1 Descriptive Statistic and Demographic Analysis

Descriptive statistics of the independent and dependent variables are presented in Table 2. Only kidney transplant recipients who met the inclusion/exclusion criteria (n =168,081) are included in this study.

Kidney Data Analysis Using SAS Software

A statistical analysis software (SAS) application was used for data analysis in this study. There were 16 variables analyzed for descriptive analysis including: 1) recipient age 2) donor age 3) recipient gender 4) donor gender 5) recipient ethnicity 6) donor ethnicity 7) recipient hepatitis C virus (HCV) sero-status 8) recipient hepatitis B virus (HBV) Surface Antigen 9) recipient Body Mass Index (BMI) 10) recipient total serum albumin 11) kidney cold ischemic time (CIT) 12) mode of kidney delivery (on ice or pump)13) deceased donor's heart beating status (heart beating or non-heart beating) 14) graft survival time 15) patient survival time 16) deceased donor blood urea nitrogen (BUN) level. Based on the above variables, the SAS analyses suggest the following:

1) Dependent Variables

a. Graft Survival Time

The distribution of graft survival time (years) data (n = 167,879) are shown in figure 1. The results suggest that the mean is 5.22 years with 95% confidence interval limits for the population mean between 5.20 and 5.24, where median = 4.04, mode = 0.00, standard deviation = 4.48, minimum = 0 and maximum = 25.54.

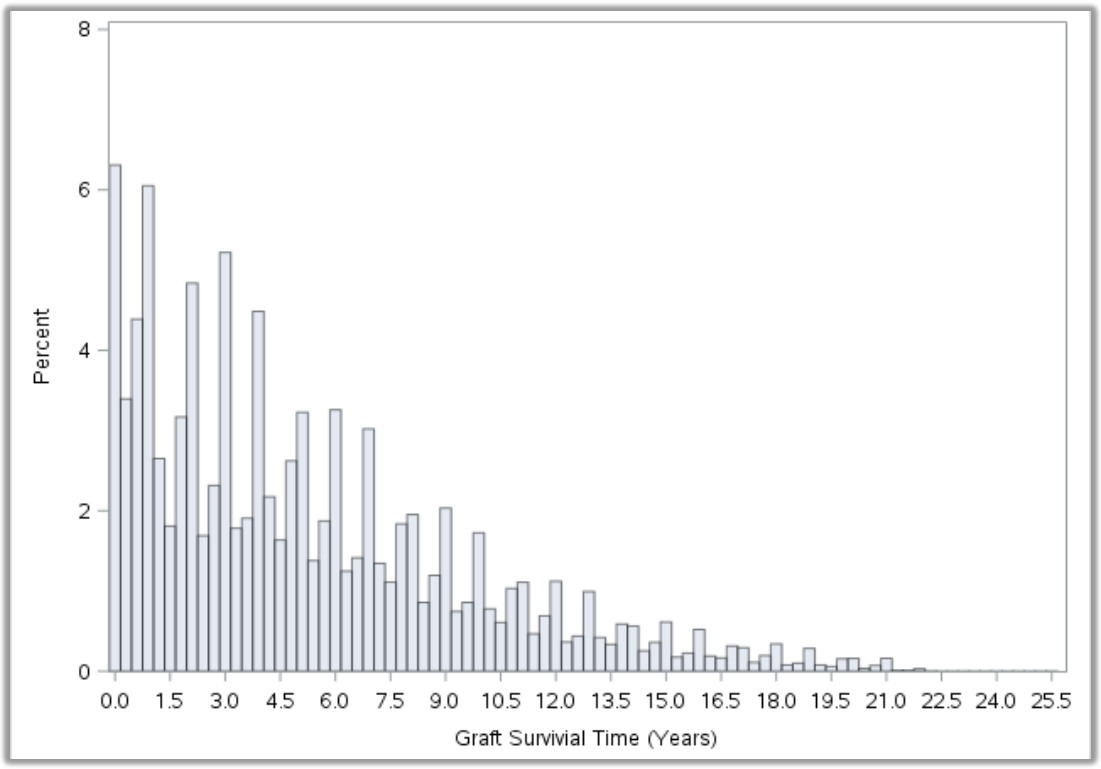

Figure 1: Distribution of Graft Survival Time in Years

b. Patient Survival Time

The distribution of patient survival time (years) data (n = 167,880) are shown in figure 2. The results suggest that the mean is 5.92 years with 95% confidence interval limits for the population mean between 5.90 and 5.95, where median = 4.96, mode = 0.01, standard deviation = 4.68 minimum = 0 and maximum = 25.54.

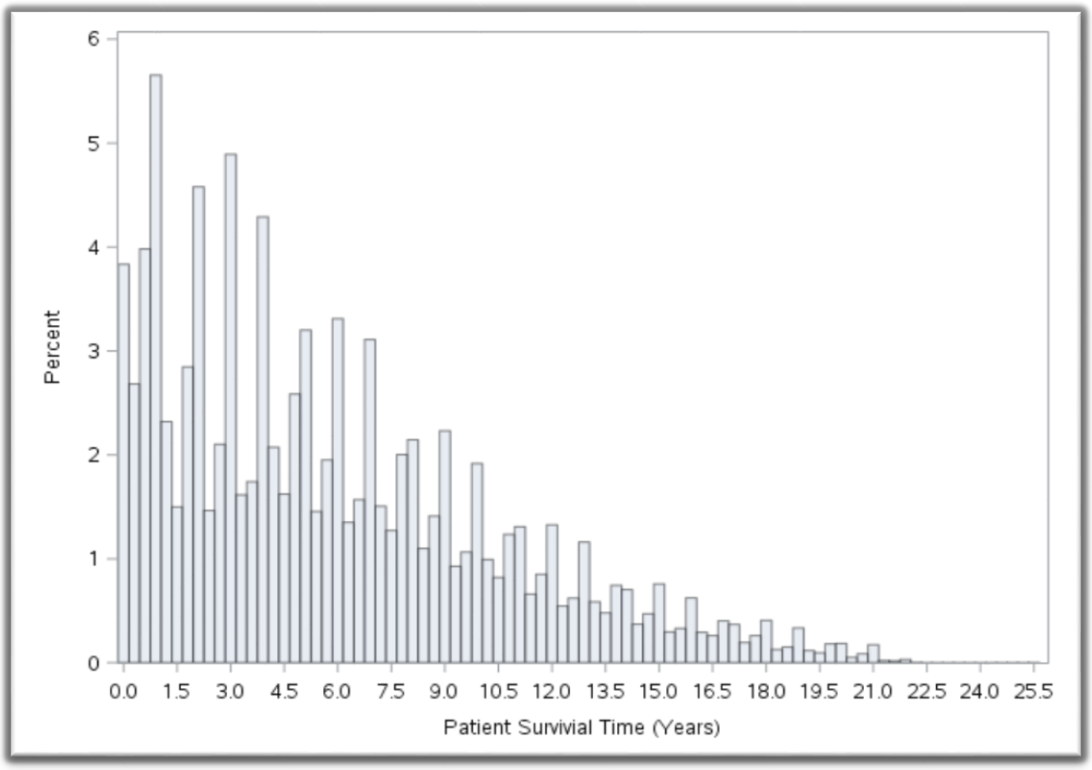

Figure 2: Distribution of Patient Survival Time in Years

2) **Independent Variable**

a. Deceased Donor Blood Urea Nitrogen (BUN) Level

I. The Original Variable of Deceased Donor BUN level

The distribution of deceased donor BUN level data (n = 168,081) are shown in figure 3. The results suggest that the mean is 15.57 mg/dl with 95% confidence interval limits for the population mean between 15.51 and 15.62, where median = 13, mode = 10, standard deviation = 11.30, minimum = 0.1 and maximum = 250.

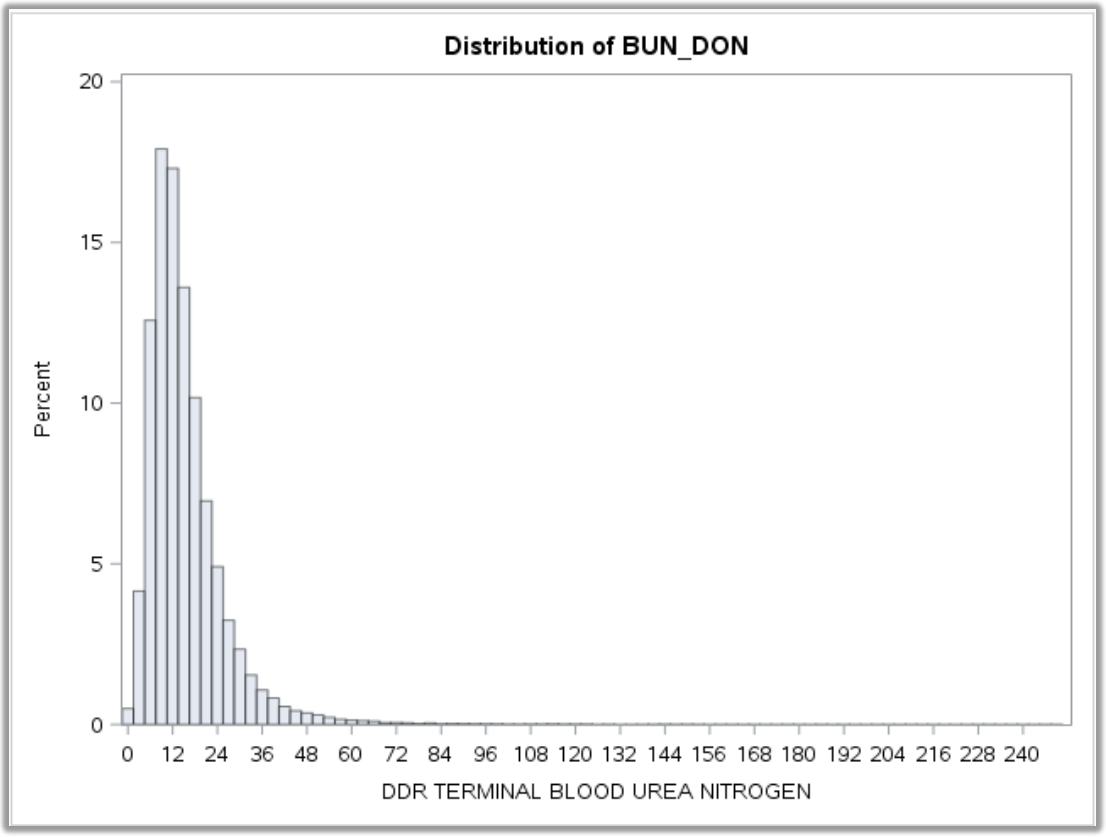

Figure 3: Distribution of Original Variable of Deceased Donor BUN level

II. The Preprocessing Variable of Deceased Donor BUN level (log)

Distribution of preprocessing deceased donor BUN level data (n = 168,081) are shown in figure 4. The results suggest that the mean log deceased donor BUN is 2.55 mg/dl with 95% confidence interval limits for the population mean between 2.54 and 2.55, where median = 2.56, mode = 2.30, standard deviation = 0.63, minimum = -2.30 and maximum = 5.52.

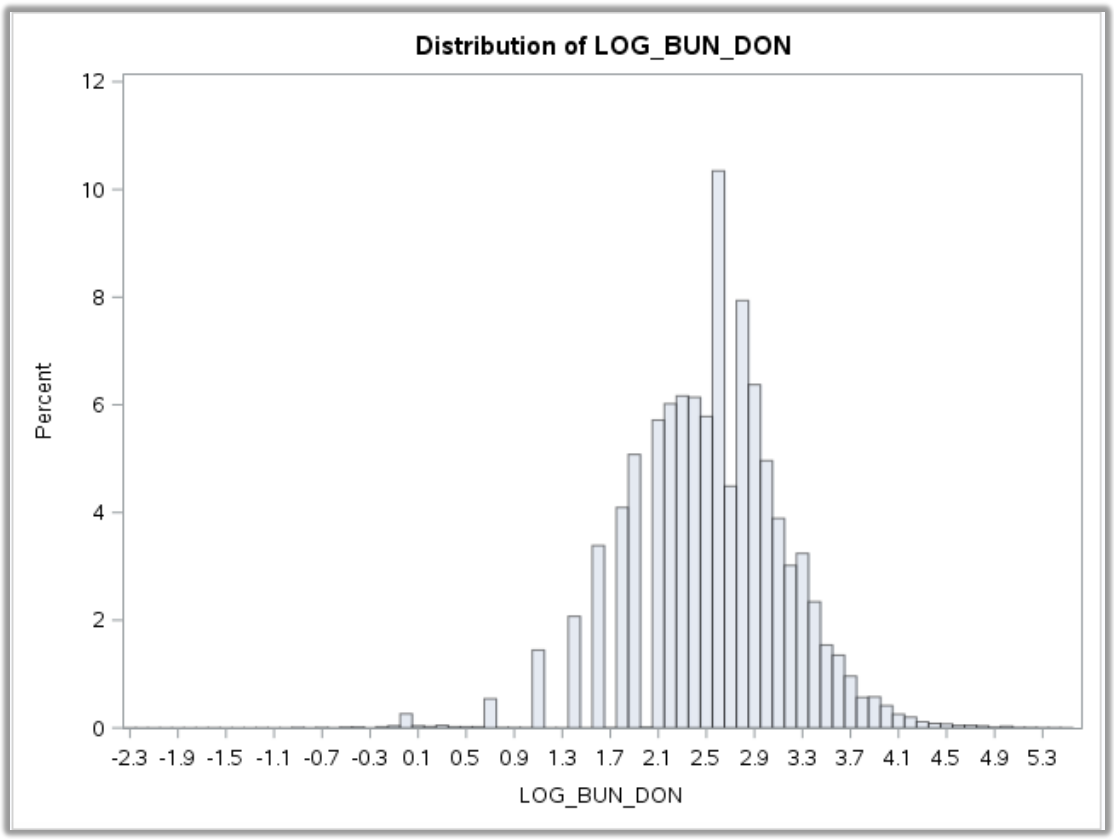

Figure 4: Distribution of Log Variable of Deceased Donor BUN level

III. Log Deceased Donor BUN level Categories

Distribution of preprocessing deceased donor BUN data (n = 168,081) are shown in figure 5. The results suggest that deceased donor from kidney with medium level of BUN (1.91 - 2.79 mg/dl) is the most common donor seen in the data, followed by deceased donor from kidney with high level of BUN (> 2.79 mg/dl) and deceased donor with low level of BUN (< 1.93 mg/dl); 53.89% (90,581), 33.97% (57,092), and 12.14% (20,408) respectively.

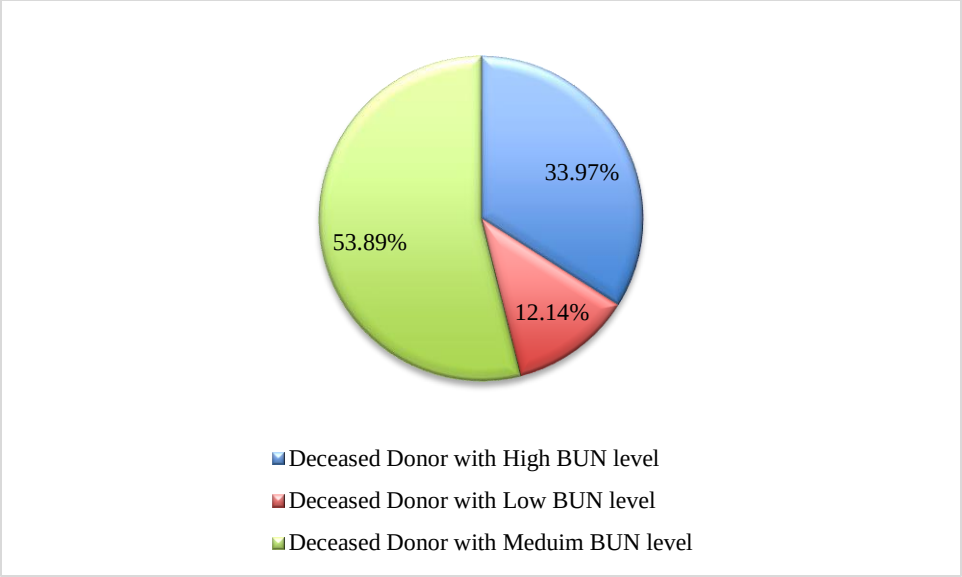

Figure 5: Log Deceased Donor BUN Level Categories

3) Confounding Variables

a. Recipient Age

The distribution of recipient age data (n = 168,081) suggests that recipients aged 50 - 59 years are most frequently seen in kidney recipients, followed by 60 - 69 years, 40 - 49 years, 30 - 39 years, 18 - 29 years, and ≥ 70 years; 27.94%, 23.74%, 21.73%, 13.21, 6.74%, and 6.64% respectively.

b. Donor Age

The distribution of donor age data (n = 168,081) suggests that donors aged 18 - 29 years and 40 - 49 years' groups are the highest majority of kidney donors, then follow 50

- 59 years, 30 - 39 years, 0 - 17 years, 60 - 69 years, ≥ 70 years; 21.62%, 21.15%, 19.48%, 15.04%, 12.97%, 8.20%, and 1.18% respectively.

c. Recipient Gender

The distribution of recipient gender data (n = 168,081) suggests that there are more male than female recipients; 60.66% (101,953) and 39.34% (66,128) respectively.

d. Donors Gender

The distribution of donor gender data (n = 168,081) suggests that there are more male donors than female donors; 59.52 (100,037) % and 40.48% (68,044) respectively.

e. Recipient Ethnicity

The distribution of recipients' ethnicity data (n =168,081) suggests that the majority of kidney recipient population is White, followed by Black, Hispanic, and other race; 46.81%, 31.45%, 13.84%, and 7.90% respectively.

f. Donor Ethnicity

The distribution of donor ethnicity data (n = 168,081) suggests that the majority of kidney donor population is White, followed by Hispanic, Black, and much lower in other race; 71.54%, 12.45%, 12.47%, and 3.53% respectively.

g. Recipient HCV Sero-Status

The distribution of HCV sero-status data (n = 162,665) suggests that the majority of HCV sero-statuses are negative and much less in positive, and not done test; 90.75%, 5.97%, and 3.27% respectively.

h. Recipient HBV Surface Antigen

The distribution of HBV surface antigen data (n = 160,864) suggests that the majority of HBV surface antigen are negative and much less in positive and not done test; 96.60%, 2.03%, and 1.34% respectively.

i. Recipient Total Serum Albumin

The distribution of recipient total serum albumin data (n = 168,081) suggests that recipients with serum albumin 4.0 - 5.49 g/dl are the majority of kidney recipients, followed by 3.5 - 3.99 g/dl, < 3.5 g/dl, and much less in recipients with serum albumin > 5.5 g/dl; 29.88%, 19.22%, 9.83%, and 0.25% respectively.

j. Recipient Body Mass Index (BMI)

The distribution of recipient BMI data (n = 168,081) suggests that recipients with BMI < 30 kg/m^2 are the majority of kidney recipients, followed by 30 - 35 kg/m^2, 35 - 40 kg/m^2 and much less recipients with BMI > 40 kg/m^2 ; 68.30%, 20.58%, 7.84%, and 1.83% respectively.

k. Kidney Cold Ischemia Time (CIT)

The distribution of kidney CIT data (n = 168,081) suggests that kidney CIT < 16 hours most frequent in kidney recipients, followed by 16 - 24 hour, 24 - 36 hour and > 36 hour; 37.55%, 35.21%, 18.24%, and 3.53% respectively.

l. Mode of Kidney Delivery (on ice or pump)

The distribution of kidney received on ice or pump data (n = 100,016) suggests that kidney received on ice are most frequent in kidney recipients, followed by kidney received on pump; 75.85% and 24.51% respectively.

m. Deceased Donor's Heart Beating Status (Heart Beating or non-Heart Beating)

The distribution of deceased donor heart beating status data (n = 168,064) suggests that deceased donor heart beating is most frequent in kidney recipients, followed by deceased donor non-heart beating; 90.35%, 9.65% respectively.

Table 2
Characteristic of Study Population (n = 168,081)

Variables	Total
Recipient age groups, *n (%)*	
18 - 29 y	11,323 (6.74)
30 - 39 y	22,205 (13.21)
40 - 49 y	36,523 (21.73)
50 - 59 y	46,964 (27.94)
60 - 69 y	39,908 (23.74)
≥ 70 y	11,158 (6.64)
Donor age groups, *n (%)*	
0 -17 y	21,798 (12.97)
18 - 29 y	36,342 (21.62)
30 - 39 y	25,283 (15.04)
40 - 49 y	35,549 (21.15)
50 - 59 y	33,346 (19.48)
60 - 69 y	13,782 (8.20)
≥ 70 y	1,981 (1.18)
Recipient gender, *n (%)*	
Female	66,128 (39.34)
Male	101,953 (60.66)
Donor gender, *n (%)*	
Female	68,044 (40.48)
Male	100,037 (59.52)
Recipient race, *n (%)*	
White	78,685 (46.81)
Black	52,861 (31.45)
Hispanic	23,264 (13.84)
Other	13,271 (7.90)

Donor race, *n (%)*	
White	120,253 (71.54)
Black	20,955 (12.47)
Hispanic	20,933 (12.45)
Other	5,940 (3.53)
HCV Sero-status, *n (%)*	
Negative	147,622 (90.75)
Not done	5,327 (3.27)
Positive	9,716 (5.97)
HBV surface antigen, *n (%)*	
Negative	155,392 (96.60)
Not done	2,211 (1.37)
Positive	3,261 (2.03)
Deceased donor non-heart beating, *n (%)*	
No	151,842 (90.35)
Yes	16,222 (9.65)
Total serum albumin, *n (%)*	
< 3.5 g/dl	16,521 (9.83)
3.5 - 3.99 g/dl	32,299 (19.22)
4.0 - 5.49 g/dl	50,219 (29.88)
> 5.5 g/dl	427 (0.25)
Recipient BMI (kg/m^2), *n (%)*	
BMI < 30	114,802 (68.30)
BMI 30 - 35	34,597 (20.58)
BMI 35 - 40	13,174 (7.84)
BMI > 40	3,084 (1.83)
Kidney cold ischemic time, *n (%)*	
< 16 h	63,116 (37.55)
16 - 24 h	59,187 (35.21)
24 - 36 h	30,657 (18.24)
> 36 h	5,933 (3.53)

Kidney received on ice or pump, *n (%)*	
Ice	75,863 (75.85)
Pump	24,153 (24.51)
Graft survival time, n (mean/SD)	167,879 (5.22/4.48)
Patient survival time, n (mean/SD)	167,880 (5.92/4.68)

Note. Percentages may not equal 100 due to missing data

Table 2: Characteristic of Study Population

4.2 Inferential Statistics

Characteristic of study population according to deceased donor BUN level (n = 168,081) are shown in table 3. A chi-square test was used to examine the association between categorical variables. ANOVA test was used to examine differences between means. Analysis of baseline patient characteristics revealed significant differences in recipient populations within the spectrum of the log deceased donor blood urea nitrogen (BUN) levels.

4.2.1 Inferential Statics for Continues Variables

a. Graft Survival Time by Deceased Donor BUN Level

ANOVA test results revealed that patients with high log deceased donor BUN level (n = 56,977) had the lowest mean 4.54; (SD = 4.13) graft survival time and patients with low log deceased donor BUN level (n = 20,393) had the highest mean 6.03; (SD = 4.80) graft survival time. The mean of medium levels of deceased donor BUN level (n = 90,509) was mean 5.46 (SD = 4.55). The F value for deceased donor BUN level is 1,132.48 with $P < 0.0001$. The p value suggested that the mean of graft survival is different in at least one log deceased donor BUN level compared to other levels. There is a statistically significant variation between the means of the graft survival time across three different levels. In addition to the statistically significant there is also a clinically significant between high deceased donor BUN level and low deceased donor BUN level. The changes are more about one year (1.49 year). As well as between medium deceased donor BUN level and low deceased donor BUN level. The difference is not big but still clinically significant. The changes about half a year (0.57 years) (figure 6).

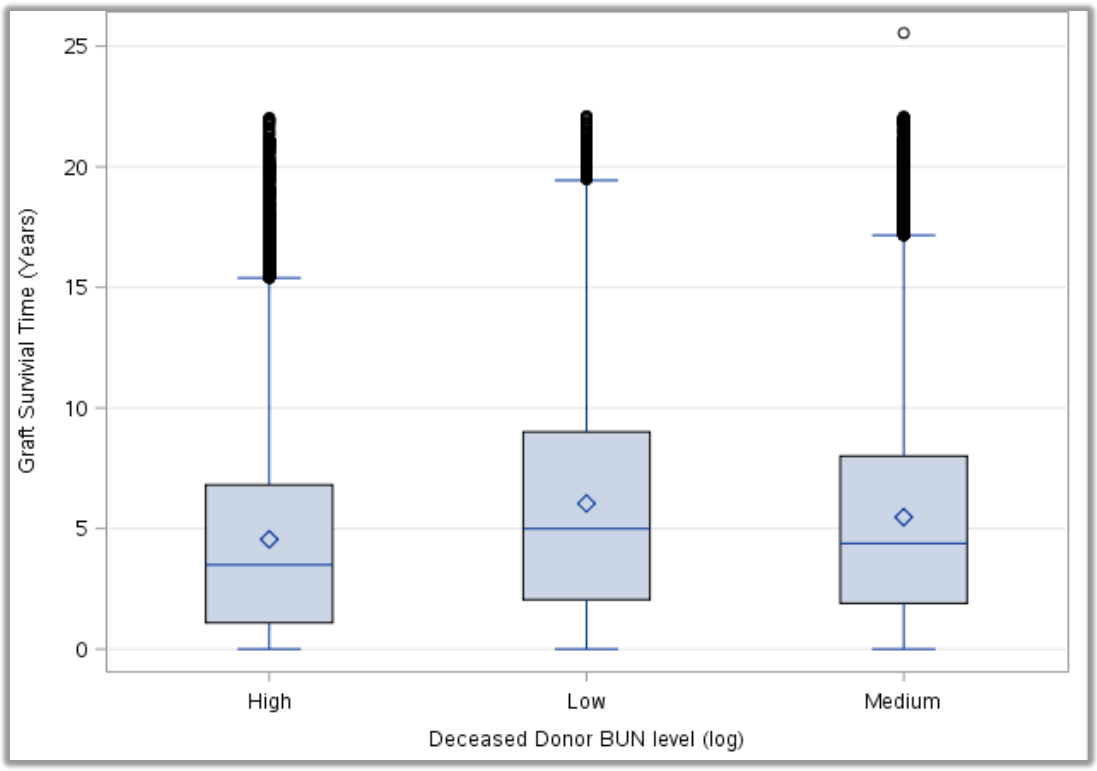

Figure 6: Graft Survival Time by Deceased Donor BUN level

b. Patient Survival Time by Deceased Donor BUN Level

ANOVA test results revealed that patients with high log deceased donor BUN level (n = 56,978) had the lowest mean 5.13 (SD = 4.37) patient survival time and patients with low log deceased donor BUN level (n = 20,393) had the highest mean 6.92 (SD = 4.93) patient survival time. Medium levels of log deceased donor BUN (n = 90,509) mean 6.20 (SD = 4.74). The F value for deceased donor BUN level is 1,454.71 with $P < 0.0001$. The p value suggested that the mean of patient failure is different in at least one log deceased donor BUN level compared to other levels. There is a statistically significant difference between the means of the patient survival time across three different levels. Moreover,

there is a clinically significant difference between high deceased donor BUN level vs. low deceased donor BUN level. The changes are more about one year (1.79 year). Even between medium deceased donor BUN level vs. low deceased donor BUN level. The difference is not big but still clinically significant. The changes about 0.72 years (figure 7).

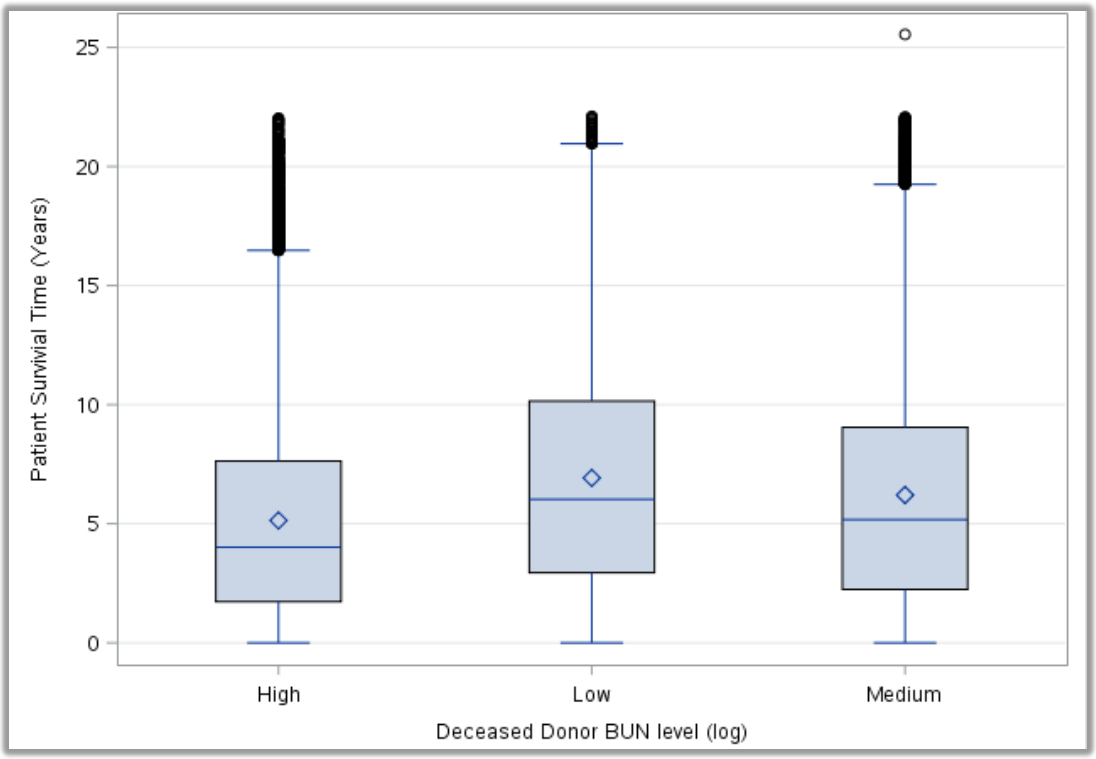

Figure 7: Patient Survival Time by Deceased Donor BUN level

4.2.2 Inferential Statics for Categorical Variables

a. Recipient Age by Deceased Donor BUN Level

The proportion of patients with high log deceased donor BUN level increases with increased recipient age. The proportion of patients with low and medium log deceased donor BUN level decreases with increased recipient age.

Chi-square analysis test showed that: (X^2 = 1,069.2348; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between recipient age and log deceased donor BUN level.

b. Donor Age by Deceased Donor BUN Level

The proportion of patients with high log deceased donor BUN level increases with increased donor age. The proportion of patients with low log deceased donor BUN level decreases with increased donor age and then slightly increased with donor age 30 - 39 years and then the proportion decreases with increased donor age. The proportion of patients with medium log deceased donor BUN level increased with donor age 18 - 29 years and then decreases with increased donor age and then increased again with increases donor age. Chi-square analysis test showed that: (X^2 = 5,359.06; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between donor age and log deceased donor BUN level.

c. Recipient Gender by Deceased Donor BUN Level

The proportion of patients with high log deceased donor BUN level is higher among male recipient 34,889 (34.22%) vs 22,203 (33.58%). The proportion of patients with low

log deceased donor BUN level is higher among female recipient. While no much differences in the proportion of patients with medium log deceased donor BUN level among female and male recipient. ($X^2 = 27.92$; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between recipient gender and log deceased donor BUN level.

d. Donor Gender by Deceased Donor BUN Level

The proportion of patients with high log deceased donor BUN level is higher among male donor. The proportion of patients with low and medium log deceased donor BUN level is higher among female donor. Chi-square analysis test showed that: ($X^2 = 4{,}393.64$; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between donor gender and log deceased donor BUN level.

e. Recipient Ethnicity by Deceased Donor BUN Level

The proportion of patients with high log deceased donor BUN level is higher among recipient with Hispanic and other race. The proportion of patients with low and medium log deceased donor BUN level is slightly higher among recipient with White race. Chi-square analysis test showed that: ($X^2 = 374.89$; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between recipient ethnicity and log deceased donor BUN level.

f. **Donor Ethnicity by Deceased Donor BUN Level**

The proportion of patients with high and low log deceased donor BUN level is higher among donor with Hispanic and other race. The proportion of patients with medium log deceased donor BUN level is higher among donor with White race. Chi-square analysis

test showed that: ($X^2 = 178.07$; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between donor ethnicity and log deceased donor BUN level.

g. Recipient HCV Sero-Status by Deceased Donor BUN Level

The proportion of patients with high, low, and medium log deceased donor BUN level is higher among not done and positive recipient HCV sero-status. Chi-square analysis test showed that: ($X^2 = 55.28$; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between recipient HCV sero-status types and log deceased donor BUN level.

h. Recipient HBV Surface Antigen by Deceased Donor BUN Level

The proportion of patients with high log deceased donor BUN level is higher among positive recipient HBV surface antigen. There is no much differences in the proportion of low log deceased donor BUN level among all recipient HBV surface antigen, negative, not done, and positive. The proportion of patients with medium log deceased donor BUN level is higher among not done recipient HBV surface antigen. Chi-square analysis test showed that: ($X^2 = 10.52$; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between recipient HBV surface antigen types and log deceased donor BUN level.

i. Recipient Serum Albumin Levels by Deceased Donor BUN Level

The proportion of patients with high and low log deceased donor BUN level increases with increased recipient serum albumin level and then started to decrease with serum albumin of > 5.5 g/dl. The proportion of patients with medium log deceased donor BUN level is higher among recipient serum albumin level of > 5.5 g/dl. Chi-square analysis

test showed that: (X^2 = 1,823.98; *P < 0.0001*). *P < 0.0001* indicates that there is a significant association between recipient serum albumin level and log deceased donor BUN level.

j. Recipient BMI by Deceased Donor BUN Level

The proportion of patients with high log deceased donor BUN level increases with increased recipient BMI and then started to decreased with BMI of > 40 kg/m^2. The proportion of patients with low log deceased donor BUN level decreases with increased recipient BMI and then started to slightly increased with BMI of > 40 kg/m^2. There is no much differences in the proportion of medium log deceased donor BUN level among recipient BMI classifications. Chi-square analysis test showed that: (X^2 = 281.78; *P < 0.0001*). *P < 0.0001* indicates that there is a significant association between recipient BMI and log deceased donor BUN level.

k. Kidney CIT by Deceased Donor BUN Level

The proportion of patients with high log deceased donor BUN level increases with increased CIT. The proportion of patients with low log deceased donor BUN level increases with increased CIT and then started to decreased with CIT of > 36 hour. The proportion of patients with medium log deceased donor BUN level decreases with increased CIT. Chi-square analysis test showed that: (X^2 = 320.91; *P <.0001*). *P < 0.0001* indicates that there is a significant association between kidney CIT and log deceased donor BUN level.

l. Mode of Kidney Delivery (on ice or pump) by Deceased Donor BUN Level

The proportion of high log deceased donor BUN level is higher among kidney received on pump vs. ice. The proportion of low and medium log deceased donor BUN level is higher among kidney received on ice vs. pump. Chi-square analysis test showed that; (X^2 = 503.15; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between mode of kidney delivery and log deceased donor BUN level.

m. Deceased Donor's Heart Beating status (non-heart beating or heart Beating) by Deceased Donor BUN Level

The proportion of high log deceased donor BUN level is higher among deceased donor's non-heart beating. The proportion of low and medium log deceased donor BUN level is higher among deceased donor's heart beating. Chi-square analysis test showed that (X^2 = 726.21; $P < 0.0001$). $P < 0.0001$ indicates that there is a significant association between deceased donor's heart beating status and log deceased donor BUN level.

Table 3
Characteristic of Study Population According to Deceased Donor BUN level (n = 168 081)

Variables	HDD BUN level *(n = 56,732)*	LDD BUN level *(n = 19,535)*	MDD BUN level *(n = 77,823)*	*P*
Recipient age groups, *n (%)*				
18 - 29 y	3,278 (28.95)	1,732 (15.30)	6,313 (55.75)	<0.0001
30 - 39 y	6,799 (30.62)	3,218 (14.49)	12,188 (41.89)	
40 - 49 y	11,580 (31.71)	4,866 (13.32)	20,077 (54.97)	
50 - 59 y	15,964 (33.99)	5,665 (12.06)	25,335 (53.95)	
60 - 69 y	14,919 (37.38)	3,989 (10.00)	21,000 (52.62)	
≥ 70 y	4,552 (40.80)	938 (8.41)	5,668 (50.80)	
Donor age groups, *n (%)*				
0 - 17 y	4,784 (21.95)	5,304 (24.33)	11,710 (53.72)	<0.0001
18 - 29 y	10,953 (30.14)	4,372 (12.03)	21,017 (57.83)	
30 - 39 y	8,710 (34.45)	3,100 (12.26)	13,473 (53.29)	
40 - 49 y	13,233 (37.22)	3,837 (10.79)	18,479 (51.98)	
50 - 59 y	13,160 (39.47)	2,836 (8.50)	17,350 (52.03)	
60 - 69 y	5,477 (39.74)	847 (6.15)	7,458 (54.11)	
≥ 70 y	775 (39.12)	112 (5.65)	1,094 (55.22)	
Recipient gender, *n (%)*				
Female	22,203 (33.58)	8,362 (12.65)	35,563 (53.78)	<0.0001
Male	34,889 (34.22)	12,046 (11.82)	55,018 (53.96)	
Donor gender, *n (%)*				
Female	17,959 (26.39)	11,638 (17.10)	38,447 (56.50)	<0.0001
Male	39,133 (39.12)	8,770 (8.77)	52,134 (52.11)	
Recipient race, *n (%)*				
White	25,141 (31.95)	9,964 (12.66)	43,580 (55.39)	<0.0001
Black	18,201 (34.43)	6,210 (11.75)	28,450 (53.82)	
Hispanic	8,760 (37.65)	2,719 (11.69)	11,785 (50.66)	
Other	4,990 (37.60)	1,515 (11.42)	6,766 (50.98)	
Donor race, *n (%)*				
White	40,190 (33.42)	14,200 (11.81)	65,863 (54.77)	<0.0001
Black	7,145 (34.10)	2,631 (12.56)	11,179 (53.35)	

Hispanic	7,607 (36.34)	2,787 (13.31)	10,539 (50.35)	
Other	2,150 (36.20)	790 (13.30)	3,000 (50.51)	
HCV Sero-status, *n (%)*				
Negative	50,808 (34.42)	17,663 (11.97)	79,151 (53.62)	<0.0001
Not done	1,684 (31.61)	671 (12.60)	2,927 (55.79)	
Positive	3,042 (31.31)	1,238 (12.74)	5,436 (55.95)	
HBV surface antigen, *n (%)*				
Negative	53,094 (34.17)	18,669 (12.01)	83,629 (53.82)	0.0325
Not done	716 (32.38)	273 (12.35)	1,222 (55.27)	
Positive	1,184 (36.31)	395 (12.11)	1,682 (51.58)	
Deceased donor non-heart beating, *n (%)*				
No	50,180 (33.05)	19,130 (12.60)	82,532 (54.35)	<0.0001
Yes	6,909 (42.59)	1,276 (7.87)	8,037 (49.54)	
Total serum albumin, *n (%)*				
< 3.5 g/dl	5,886 (35.63)	1,853 (11.22)	8,782 (53.16)	<0.0001
3.5 - 3.99 g/dl	11,831 (36.63)	3,346 (10.36)	17,122 (53.01)	
4.0 - 5.49 g/dl	19,493 (38.82)	4,996 (9.95)	25,730 (51.24)	
> 5.5 g/dl	141 (33.02)	54 (12.65)	232 (54.33)	
Recipient BMI (kg/m^2**), *n (%)***				
BMI < 30	38,133 (33.22)	14,736 (12.84)	61,933 (53.95)	<0.0001
BMI 30 - 35	12,408 (35.86)	3,687 (10.66)	18,502 (53.48)	
BMI 35 - 40	4,789 (36.35)	1,312 (9.96)	7,073 (53.69)	
BMI > 40	1,074 (34.82)	3,29 (10.67)	1,681 (54.51)	
Kidney cold ischemic time, *n (%)*				
< 16 h	21,097 (33.43)	7,502 (11.89)	34,517 (54.69)	<0.0001
16 - 24 h	20,068 (33.91)	7,211 (12.18)	31,908 (53.91)	
24 - 36 h	10,723 (34.98)	3,815 (12.44)	16,119 (52.58)	
> 36 h	2,513 (42.36)	608 (10.25)	2,812 (47.40)	

Kidney received on ice or pump, *n (%)*				
Ice	28,403 (37.44)	7,632 (10.06)	39,828 (52.50)	<0.0001
Pump	10,896 (45.11)	1,783 (7.38)	11,474 (47.51)	

Note. Percentages may not equal 100 due to missing data

Table 3: Characteristic of Study Population According to Deceased Donor BUN Level

Table 4 and 5 displays graft and patient survival rates among independent and confounding subgroups. In all subgroups, graft survival and patient survival were statistically significant (*P < 0.0001*). For data analysis, ANOVA and t-test were used.

a. Deceased Donor BUN level

ANOVA test results revealed that recipients with low log deceased donor BUN level (< 1.93 mg/dl) had better mean graft and patient survival times and recipients with high log deceased donor BUN level (> 2.79 mg/dl) had the lowest mean graft and patient survival times. *P < 0.0001* indicates that the mean of graft and patient survival time is different in at least one deceased donor BUN level compared to other levels. There was a statistically significant difference in the means of the graft survival and patient survival variables across different log deceased donor BUN level.

b. Recipient Age

ANOVA test results revealed that recipients aged 30 - 39 years had better mean graft and patient survival times, while recipients aged ≥ 70 years had the lowest mean graft and patient survival times. *P < 0.0001* indicates that the mean of graft and patient survival

time is different in at least one recipient age groups compared to other recipient groups. There was a statistically significant difference in the means of the graft survival and patient survival variables across different recipient age groups.

c. Donor Age

ANOVA test results revealed that donors aged 0 - 17 years had better mean graft and patient survival times, while donors aged ≥ 70 years had the lowest mean graft and patient survival times. $P < 0.0001$ indicates that the mean of graft and patient survival time is different in at least one donor age groups compared to other donor groups. There was a statistically significant difference in the means of the graft survival and patient survival variables across different donor age groups.

d. Recipient Gender

Two sample t-test result indicated that the mean graft and patient survival time among female patients is higher compare to male patients, or in other word, female recipient had better mean graft and patient survival times compared to male patients. $P < 0.0001$ indicates that there was a statistically significant difference in the means of the graft survival time and patient survival time between male and female recipients.

e. Donor Gender

Two sample t-test result indicated that the mean graft and patient survival time among male donors is higher compare to female donors, or in other word, male donors had better mean graft and patient survival times compared to female donors. $P < 0.0001$

indicates that there was a statistically significant difference in the means of the graft survival time and patient survival time between male and female donor.

f. Recipient Ethnicity

ANOVA test results revealed that patients with White race had better mean graft and patient survival time, and patients with Black race had lowest mean graft and patient survival time. $P < 0.0001$ indicates that the mean of graft and patient survival time is different in at least one recipient ethnicity groups compared to other recipient ethnicity groups. There was a statistically significant difference in the means of the graft survival and patient survival variables across the different recipient ethnicity groups.

g. Donor Ethnicity

ANOVA test results revealed that recipients who received kidney from donors with White race had better mean graft and patient survival time, and recipients who received kidney from donors with Black race had lowest mean graft survival time. While recipients who received kidney from other race had lowest, mean patient survival time. $P < 0.0001$ indicates that the mean of graft and patient survival time is different in at least one-donor ethnicity groups compared to other donor ethnicity groups. There was a statistically significant difference in the means of the graft survival and patient survival variables across the different donor ethnicity groups.

h. HCV Sero-Status

ANOVA test results revealed that patients with not done HCV sero-status test had better mean graft and patient survival time, and patients with positive HCV sero-status test had lowest mean graft and patient survival time. $P < 0.0001$ indicates that the mean of graft and patient survival time is different in at least one HCV sero-status groups compared to other HCV sero-status groups. There was a statistically significant difference in the means of the graft survival and patient survival variables across the different HCV sero-status groups.

i. HBV Surface Antigen

ANOVA test result revealed that patients with not done HBV surface antigen test had better mean graft and patient survival times, and patients with positive HBV surface antigen had lowest mean graft and patient survival time. $P < 0.0001$ indicates that the mean of graft and patient survival time is different in at least one HBV surface antigen groups compared to other HBV surface antigen groups. There was a statistically significant difference in the means of the graft survival and patient survival variables across the different HBV surface antigen groups.

j. Deceased Donor's Heart Beating Status (Heart Beating or non-Heart Beating)

Two sample t-test result indicated that the mean graft and patient survival time among patient with deceased donor with heart beating is higher compare to deceased donor

with non-heart beating, or in other word, deceased donor with heart beating had better mean graft and patient survival times compared to deceased donor with non-heart beating. *P < 0.0001* indicates that there was a statistically significant difference in the means of the graft survival time and patient survival time between heart beating deceased donor and non-heart beating deceased donor.

k. Recipient Total Serum Albumin Level

ANOVA test results revealed that patients with > 5.5 g/dl serum albumin level had better mean graft and patient survival time, and patients with 4.0 - 5.49 g/dl serum albumin had the lowest mean graft and patient survival time. *P < 0.0001* indicates that the mean of graft and patient survival time is different in at least one recipient serum albumin level compared to other serum albumin level. There was a statistically significant difference in the means of the graft survival and patient survival variables across the different recipient serum albumin level.

l. Recipient BMI

ANOVA test results revealed that non- obese recipients with BMI < 30 kg/m^2 had better mean graft and patient survival time, and obese class II patients with BMI 35 - 40 kg/m^2 had lowest mean graft and patient survival time. *P < 0.0001* indicates that the mean of graft and patient survival time is different in at least one recipient BMI categorizes compared to other BMI categorizes. There was a statistically significant difference in the means of the graft survival and patient survival variables across the different recipient BMI categorizes.

m. Kidney Donor CIT

ANOVA test results revealed that recipient received kidneys with CIT with 24 - 36 hour had better mean graft and patient survival time, and recipient received kidneys with CIT > 36 hour had the lowest mean graft survival time, and kidneys with CIT < 16 hour had the lowest mean patient survival time. *P < 0.0001* indicates that the mean of graft and patient survival time is different in at least one kidneys with CIT compared to other CIT. There was a statistically significant difference in the means of the graft survival and patient survival variables across the different kidneys with CIT.

n. Mode of Kidney Delivery (on ice or pump)

Two sample t-test result indicated that the mean graft and patient survival time among kidneys received on ice is higher compare to kidneys received on pump, or in other word, kidneys received on ice had better mean graft and patient survival times compared to kidneys received on pump. $P < 0.0001$ indicates that there was a statistically significant difference in the means of the graft survival time and patient survival time between kidney received on ice and kidney received on pump.

Table 4

Graft Survival Time among Subgroups (n =168,081)

Variables	n	Graft Survival Time (years)	
		Mean (SD)	*p*
Deceased Donor BUN level, n (mg/dl)			
< 1.93	20,393	6.03 (4.80)	<0.0001
1.93 - 2.79	90,509	5.46 (4.55)	
> 2.79	56,977	4.54 (4.13)	
Recipient age groups, *n*			
18 - 29 y	11,317	5.70 (4.98)	<0.0001
30 - 39 y	22,183	5.95 (5.03)	
40 - 49 y	36,481	5.84 (4.84)	
50 - 59 y	46,913	5.29 (4.38)	
60 - 69 y	39,845	4.44 (3.80)	
≥ 70 y	11,140	3.78 (3.19)	
Donor age groups, *n*			
0 -17 y	21,778	6.15 (5.04)	<0.0001
18 - 29 y	36,298	5.68 (4.68)	
30 - 39 y	25,245	5.27 (4.53)	
40 - 49 y	35,504	5.11 (4.31)	
50 - 59 y	33,307	4.65 (4.09)	
60 - 69 y	13,768	4.28 (3.81)	
≥ 70 y	1,979	4.07 (3.69)	
Recipient gender, *n*			
Female	66,049	5.37 (4.57)	<0.0001
Male	101,830	5.13 (4.41)	
Donor gender, *n*			
Female	67,965	5.10 (4.42)	<0.0001
Male	99,914	5.30 (4.51)	
Recipient race, *n*			
White	78,627	5.69 (4.72)	<0.0001
Black	52,772	4.65 (4.08)	
Hispanic	23,220	4.97 (4.32)	
Other	13,260	5.16 (4.46)	

Donor race, *n*			
White	120,112	5.37 (4.56)	<0.0001
Black	20,923	4.68 (4.15)	
Hispanic	20,909	5.03 (4.26)	
Other	5,935	4.76 (4.30)	
HCV Sero-status, *n*			
Negative	147,600	5.18 (4.45)	<0.0001
Not done	5,327	6.00 (4.22)	
Positive	9,715	4.42 (3.92)	
HBV surface antigen, *n*			
Negative	155,369	5.15 (4.45)	<0.0001
Not done	2,211	5.95 (4.26)	
Positive	3,261	4.80 (4.04)	
Deceased donor non-heart beating, *n*			
No	151,671	5.38 (4.55)	<0.0001
Yes	16,191	3.68 (3.31)	
Total serum albumin, *n*			
< 3.5 g/dl	16,491	4.18 (3.44)	<0.0001
3.5 - 3.99g/dl	32,256	4.21 (3.42)	
4.0 - 5.49g/dl	50,106	4.08 (3.38)	
> 5.5g/dl	427	4.64 (3.76)	
Recipient BMI (kg/m^2**), n**			
BMI < 30	114,686	5.46 (4.63)	<0.0001
BMI 30 - 35	34,546	4.69 (4.03)	
BMI 35 - 40	13,143	4.35 (3.76)	
BMI > 40	3,081	4.75 (3.99)	
Kidney cold ischemic time, *n*			
< 16h	63,112	4.85 (4.15)	<0.0001
16 - 24h	59,186	5.37 (4.58)	
24 - 36h	30,657	5.42 (4.74)	
> 36h	5,933	4.77 (4.46)	

Kidney received on ice or pump, *n*			
Ice	75,855	4.07 (3.06)	<0.0001
Pump	24,148	3.19 (2.66)	

Note. Percentages may not equal 100 due to missing data.

Table 4: Graft Survival Time among Subgroups

Table 5

Patient Survival Time among Subgroups (n =168,081)

Variables	n	Patient Survival Time (years)	
		Mean (SD)	*p*
Deceased Donor BUN level, n (mg/dl)			
< 1.93	20,393	6.92 (4.93)	<0.0001
1.93 - 2.79	90,509	6.20 (4.74)	
> 2.79	56,978	5.13 (4.37)	
Recipient age groups, *n*			
18 - 29 y	11,317	6.94 (5.25)	<0.0001
30 - 39 y	22,183	6.97 (5.20)	
40 - 49 y	36,481	6.71 (5.03)	
50 - 59 y	46,913	5.92 (4.54)	
60 - 69 y	39,846	4.86 (3.95)	
≥ 70 y	11,140	4.08 (3.29)	
Donor age groups, *n*			
0 -17 y	21,778	6.97 (5.17)	<0.0001
18 - 29 y	36,298	6.30 (4.86)	
30 - 39 y	25,245	5.94 (4.78)	
40 - 49 y	35,504	5.82 (4.54)	
50 - 59 y	33,307	5.35 (4.32)	
60 - 69 y	13,769	5.07 (4.10)	
≥ 70 y	1,979	4.97 (3.95)	

Recipient gender, *n*			
Female	66,049	6.04 (4.74)	<0.0001
Male	101,831	5.85 (4.64)	
Donor gender, *n*			
Female	67,966	5.83 (4.64)	<0.0001
Male	99,914	5.99 (4.72)	
Recipient race, *n*			
White	78,627	6.35 (4.85)	<0.0001
Black	52,772	5.53 (4.42)	
Hispanic	23,221	5.53 (4.56)	
Other	13,260	5.70 (4.67)	
Donor race, *n*			
White	120,112	6.08 (4.76)	<0.0001
Black	20,923	5.47 (4.45)	
Hispanic	20,910	5.64 (4.47)	
Other	5,935	5.39 (4.52)	
HCV Sero-status, *n*			
Negative	147,600	5.83 (4.65)	<0.0001
Not done	5,327	6.65 (4.15)	
Positive	9,715	5.42 (4.37)	
HBV surface antigen, *n*			
Negative	155,369	5.84 (4.67)	<0.0001
Not done	2,211	6.65 (4.32)	
Positive	3,261	5.35 (4.23)	
Deceased donor non-heart beating, *n*			
No	151,672	6.14 (4.75)	<0.0001
Yes	16,191	3.93 (3.41)	
Total serum albumin, *n*			
< 3.5 g/dl	16,491	4.52 (3.53)	<0.0001
3.5 - 3.99g/dl	32,257	4.50 (3.49)	
4.0 - 5.49g/dl	50,106	4.34 (3.45)	
> 5.5g/dl	427	5.04 (3.89)	

Recipient BMI (kg/m^2**), n**			
BMI < 30	114,686	6.20 (4.82)	<0.0001
BMI 30 - 35	34,547	5.27 (4.25)	
BMI 35 - 40	13,143	4.90 (4.01)	
BMI > 40	3,081	5.49 (4.24)	
Kidney cold ischemic time, *n*			
< 16h	63,112	5.38 (4.37)	<0.0001
16 - 24h	59,186	6.13 (4.78)	
24 - 36h	30,657	6.29 (4.96)	
> 36h	5,933	5.54 (4.69)	
Kidney received on ice or pump, *n*			
Ice	75,855	4.29 (3.07)	<0.0001
Pump	24,148	3.34 (2.69)	

Note. Percentages may not equal 100 due to missing data.

Table 5: Patient Survival Time among Subgroups

4.3 Predictive Analytics

Two analytic approaches for survival data (time to event) were presented: Kaplan-Meier survival curves using PROC LIFETEST and the cox proportional hazards model using PROC PHREG.

4.3.1 Kaplan-Meier Estimation of the Survivor Function

Figure 8 displays the graph of the product-limit survivor function estimates versus graft survival time and figure 9 displays the graph of the product limit survivor function estimates versus patient survival time.

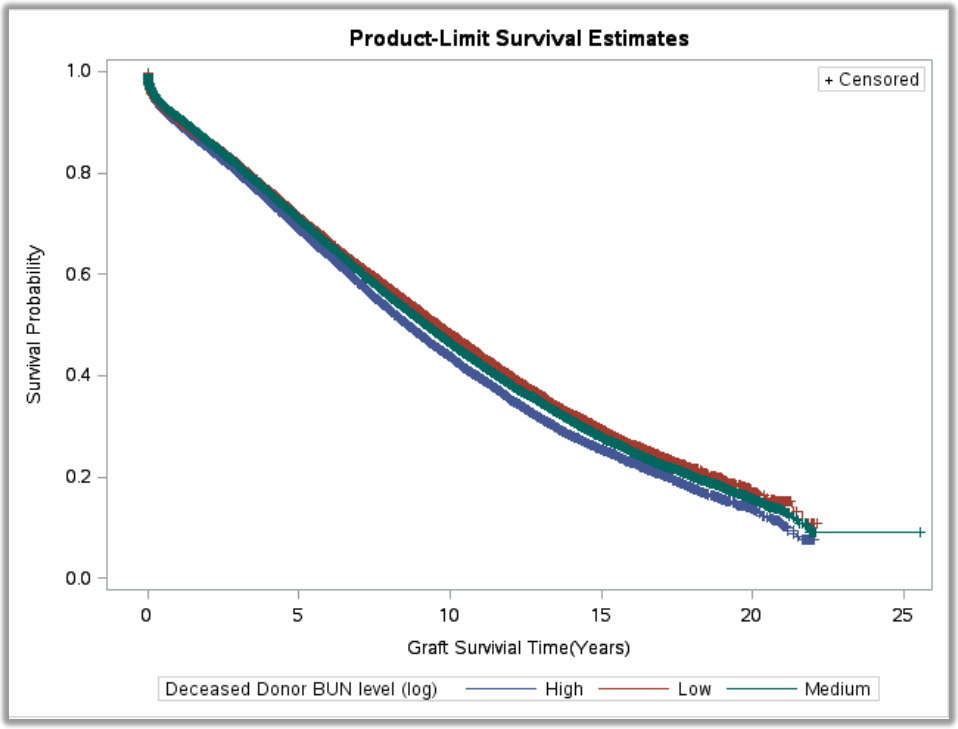

Figure 8: Kaplan-Meir Estimates of the Survivor Functions for Graft Survival by Deceased Donor BUN level

Above graph shows Kaplan-Meir curve, with the x-axis representing time-to-event in years and y-axis representing probability of survival. This survival analysis included 167,879 patients' time to graft failure following kidney transplantation, with time presented in years.

Figure 8 highlights differences in survival between deceased donor BUN level groups. For example, recipients with deceased kidney from donor with low BUN level consistently have highest survival proportion in the life-course. In addition, the probability of graft survival of recipient with high, medium, and low log deceased donor BUN level at 5 years was 68%,70%,71% respectively. The 10 year was 43%, 46%, 48% respectively, 15 year was 25%, 27%, 29% respectively, 20 year was 13%, 15%, 16% respectively, and 22 years was 7%,9%.,10% respectively. The "flat" section on the right tail of medium log

deceased donor BUN level line represents cases that are censored at graft success (right censoring if no event occurred).

The estimated time to event percentiles can be seen that the 25th percentile is 18 years, 50th percentile is 10 years, and the 75th percentile is 4.5 years for recipient with low log deceased donor BUN level.

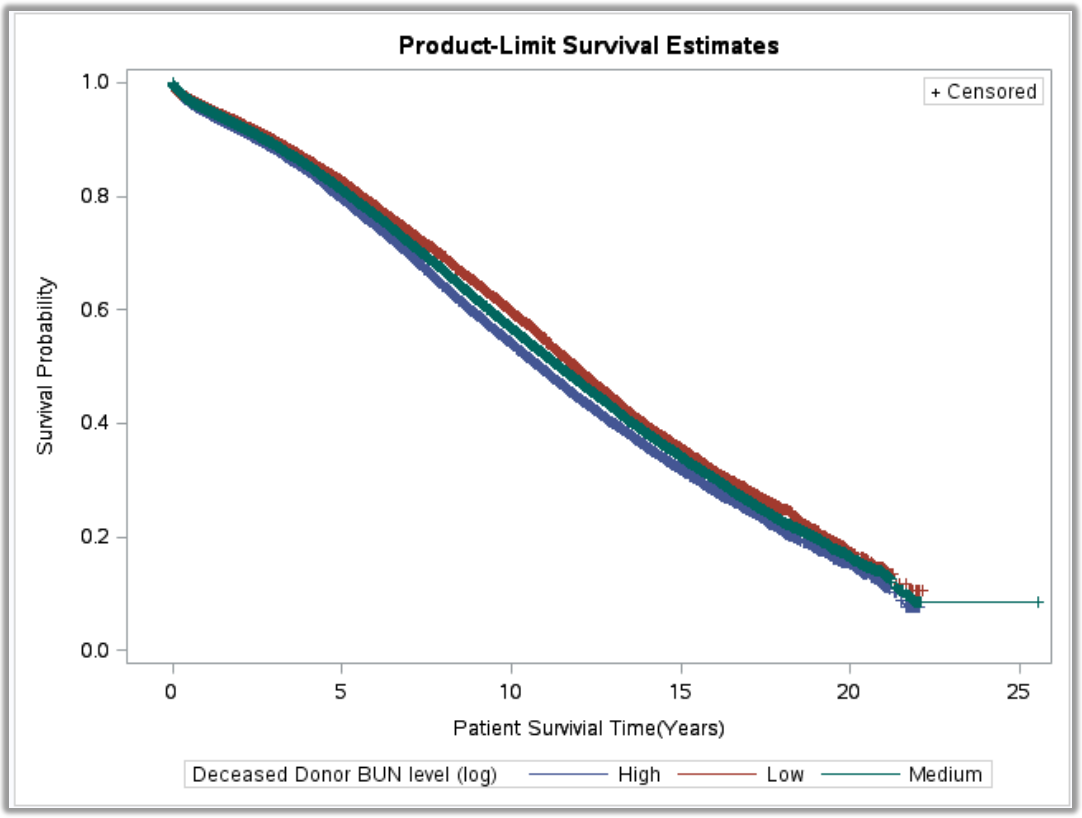

Figure 9: Kaplan-Meir Estimates of the Survivor Functions for Patient Survival by Deceased Donor BUN level

Above graph shows Kaplan-Meir curve, with the x-axis representing time-to-event in years and y-axis representing probability of survival. This survival analysis included 167,880 patients' time to death following kidney transplantation, with time presented in years.

According to the figure above the probability of patient survival of recipient with high, medium, and low log deceased donor BUN level at 5 years was 79%, 81%, 82% respectively. The 10 year was 54%, 56 %, 59% respectively, 15 year was 31%, 34%, 35% respectively, 20 year was 15%, 16%, 17% respectively, and 22 years 7%,8%,10%, retrospectively.

The estimated time to event percentiles can be seen that the 25^{th} percentile is 18 years, 50^{th} percentile is 13 years, and the 75^{th} percentile is 8 years for recipient with low log deceased donor BUN level. The conclusions were reached that recipient with high log deceased donor BUN level encountered early death and had a smaller percent surviving at any given time.

In conclusion, Kaplan-Meier analysis revealed that graft survival was significantly lower among recipient with high log deceased donor BUN level (BUN > 2.79 mg/dl) compared with subjects with low log deceased donor BUN level (BUN < 1.93 mg/dl) or medium log deceased donor BUN level (BUN 1.93 - 2.79 mg/dl). In other words, recipient with high log deceased donor BUN level encountered early graft failure and had a smaller percent surviving at any given time. Indeed, log-rank analysis showed that patient receiving deceased kidney from donor with high BUN level had a statistically significant the lowest graft survival compared with those receiving kidney from deceased donor with low BUN level or medium BUN level ($P < 0.0001$; figure 8). The *p* value shows that the significant separation between groups. In addition, it indicates that graft survival time was statistically significant affected by deceased donor BUN level but not clinically significant because the differences were very small. Patient survival was also statistically significant affected by deceased donor BUN level but not clinically significant ($P < 0.0001$; figure 9).

Table 6 displays graft and patient 5 year survival rates in recipients with high, medium, and low deceased donor BUN level within subgroups. In most subgroups, graft and patient survival were statistically significantly lower in recipients with high deceased donor BUN level compared with recipients with low and medium deceased donor BUN level ($P < 0.0001$). All the recipients ethnicity has significant differences at 5 year graft and patient survival within high, low, and medium deceased donor BUN level. White, Black and Hispanic donors ethnicity have significant differences at 5 year graft and patient survival time while donors of other races did not show any significant differences. Recipient and donor's gender have significant differences at 5-year graft and patient survival time; low BUN level has high graft and patient survival time among male and female. Patient age 18 - 29 years and ≥ 70 years has no significant difference in the graft survival at 5 years. Patient age 18 to 49 years and ≥ 70 years has no significant difference in the patient survival at 5 years. Positive HCV sero-status has no significant difference in the graft and patient survival at 5 years. Positive HBV surface antigen has no significant difference in the graft and patient survival at 5 years. Patient with > 5.5 g/dl of serum albumin has no significant difference in the graft and patient survival at 5 years. Class III obese patient with BMI > 40 kg/m^2 has no significant difference in the graft and patient survival at 5 years. Patient with CIT > 36 hour has no significant difference in the graft and patient survival at 5 years. Kidney received on ice or pump has significant difference in the graft survival at 5 years while kidney received on pump has no significant difference in patient survival at 5 years. Deceased donor heart beating and non-heart beating has significant difference in the graft survival at 5 years while deceased donor heart beating has no significant difference in patient survival at 5 years.

Table 6
5 Years Graft and Patient Survival Rates in High, Low, and Medium Deceased Donor BUN Level Within Subgroups

Subgroups	5-y Graft Survival Time%				5-y Patient Survival Time%			
	High	Medium	Low	*P*	High	Medium	Low	*P*
Recipient age groups, *n*								
18 - 29 y	66	68	66	0.09	94	93	93	0.94
30 - 39 y	72	73	73	0.02	90	90	90	0.38
40 - 49 y	73	74	75	0.0006	86	86	87	0.10
50 - 59 y	71	72	72	<.0001	79	80	80	0.03
60 - 69 y	64	67	66	<.0001	70	72	71	0.0009
≥ 70 y	58	60	60	0.08	61	62	64	0.18
Donor age groups, *n*								
0 - 17 y	75	74	73	0.75	84	85	85	0.57
18 - 29 y	76	76	75	0.49	85	85	85	0.76
30 - 39 y	74	74	73	0.24	83	83	84	0.80
40 - 49 y	69	69	69	0.09	81	80	80	0.50
50 - 59 y	63	65	66	0.0005	75	77	78	0.002
60 - 69 y	54	59	55	<.0001	66	70	69	<.0001
≥ 70 y	48	52	47	0.42	60	64	60	0.47
Recipient gender, *n*								
Female	71	72	73	<.0001	81	82	84	<.0001
Male	67	69	70	<.0001	78	80	81	<.0001
Donor gender, *n*								
Female	66	68	70	<.0001	78	79	82	<.0001
Male	70	72	72	<.0001	80	82	83	<.0001
Recipient race, *n*								
White	69	72	72	<.0001	77	79	81	<.0001
Black	63	65	65	0.0015	79	80	82	<.0001
Hispanic	74	76	75	0.0003	83	84	86	0.0058
Other	76	77	76	0.0004	83	86	85	<.0001

Donor race, *n*								
White	69	71	71	<.0001	79	80	82	<.0001
Black	62	66	67	<.0001	77	79	82	<.0001
Hispanic	70	74	74	<.0001	81	83	84	<.0001
Other	71	71	72	0.1807	80	81	82	0.0460
HCV Sero-status, *n*								
Negative	69	71	72	<.0001	80	81	83	<.0001
Not done	68	71	71	0.0006	79	81	81	0.0029
Positive	59	59	61	0.3819	74	74	75	0.4435
HBV surface antigen, *n*								
Negative	69	71	71	<.0001	79	81	82	<.0001
Not done	68	73	72	0.0081	79	84	83	0.0179
Positive	67	71	67	0.1894	78	81	80	0.2385
Deceased donor non-heart beating, *n*								
No	68	70	71	<.0001	90	82	79	<.0001
Yes	71	73	72	0.0015	81	80	81	0.0938
Total serum albumin, *n*								
< 3.5 g/dl	69	69	71	0.0142	77	77	79	0.0087
3.5 - 3.99 g/dl	70	72	72	0.0001	78	79	81	0.0004
4.0 - 5.49 g/dl	72	75	76	<.0001	82	84	86	<.0001
> 5.5 g/dl	64	73	63	0.4390	74	84	78	0.1302
Recipient BMI, n								
BMI <30 kg/m^2	69	71	72	<.0001	80	81	83	<.0001
BMI 30-35 kg/m^2	67	69	69	<.0001	78	79	81	<.0001
BMI 35-40 kg/m^2	66	68	67	0.0242	78	80	79	0.0048
BMI >40 kg/m^2	65	63	65	0.6507	79	78	82	0.9430
Kidney cold ischemic time, *n*								
< 16h	71	72	73	0.0001	81	82	84	<.0001
16 - 24 h	68	70	71	<.0001	79	80	81	<.0001
24 - 36 h	65	69	68	<.0001	77	80	81	<.0001
> 36 h	65	65	62	0.5672	78	79	79	0.2927

Kidney received on ice or pump, *n*								
Ice	72	74	75	<.0001	80	82	80	<.0001
Pump	70	71	70	0.0511	79	78	79	0.242

Note. Percentages may not equal 100 due to missing data.

Table 6: 5 Years Graft and Patient Survival Rates in High, Low, and Medium Deceased Donor BUN Level within Subgroups

4.3.2 The Cox Proportional Hazards Model Estimate Ratio of Hazard

Functions

a. Unadjusted Model for Graft Survival

This model included 167,879 patients. Hazard rate in the patient receiving deceased kidney from donor with high log BUN level was estimated to be 1.122 times more likely to experience graft failure at any time after kidney transplantation than patient receiving deceased kidney from donor with low log BUN level. In other words, patient receiving deceased kidney from donor with high BUN level had 12% higher risk of graft failure compared with those receiving deceased kidney donors with low BUN level.

This difference is statistically significant (HR = 1.122, 95% CI = [1.095-1.149], $P < 0.0001$).

Hazard rate in the patient receiving deceased kidney from donor with medium log BUN level was estimated to be 1.035 times more likely to experience graft failure at any time after kidney transplantation than patient receiving deceased kidney from donor with low log BUN level. In other words, patient receiving deceased kidney from donor with

medium log BUN level had 3% higher risk of graft failure compared with those receiving deceased kidney from donor with low log BUN level.

This difference is statistically significant (HR = 1.035, 95% CI = [1.012-1.059], *P = 0.0031*).

Furthermore, there is statistically significant difference in graft failure between patient receiving deceased kidney from donor with high and medium log deceased donor BUN level (CI = [1.06 - 1.10], *P < 0.0001*).

b. Unadjusted Model for Patient Survival

This model included 167,880 patients. Hazard rate in the patient receiving deceased kidney from donor with high log BUN level was estimated to be 1.152 times more likely to experience death at any time after kidney transplantation than patient receiving deceased kidney from donor with low log BUN level. In other words, patient receiving deceased kidney donor with high BUN level had 15% higher risk of death compared with those receiving deceased kidney donor with low log BUN level.

This difference is statistically significant (HR = 1.152, 95% HR CI = [1.121 - 1.183], *P < 0.0001*).

Hazard rate in the patient receiving deceased kidney from donor with medium log BUN level was estimated to be 1.067 times more likely to experience death at any time after kidney transplantation than patient receiving deceased kidney from donor with low log BUN level. In other words, patient receiving deceased kidney from donor with medium log BUN level had 6% higher risk of mortality compared with those receiving deceased kidney from donor with low log BUN level.

This difference is statistically significant (HR = 1.067, 95% HR CI = [1.041 - 1.094], *P < 0.0001*).

Likewise, there is statistically significant difference in mortality between patient receiving deceased kidney from donor with high and medium log deceased donor BUN level (CI = [1.05 - 1.09], *P < 0.0001*).

c. Adjusted Model for Graft Survival

This model included 97,855 patients. Hazard rate of having graft failure in-patient receiving deceased kidney from donor with high log BUN level was estimated to be 1.08 times greater than in those receiving deceased kidney from donor with low log BUN level even after adjusting for potential confounders. In other words, 8% higher incidence of graft failure for patient receiving deceased kidney from donor with high log BUN level compared with those receiving deceased kidney from donor with low log BUN level even after adjusting for potential confounders. This difference is statistically significant (HR = 1.08, 95% HR CI = [1.03 - 1.13], *P = 0.0009*). However, patient receiving deceased kidney from donor with medium log BUN level appears to be not associated with increase in risk of graft failure (HR = 1.00) and this effect did not reach significance after adjusting for potential confounders (*p = 0.9736*). (HR = 1.001, 95% HR CI = [0.95 - 1.04], *p = 0.9736*).

The conclusions were reached that the log of high BUN level of deceased kidney remained statistically significantly associated with time to graft failure compare to the log of low BUN level of deceased kidney even after adjusting for potential confounders. However, patient receiving deceased kidney from donor with medium log BUN level

appears to be not associated with increase in risk of graft failure and this effect did not reach significance after adjusting for potential confounders.

d. Adjusted Model for Patient Survival

This model included 97,855 patients. Hazard rate of death in patient receiving deceased kidney from donor with high log BUN level was estimated to be 1.064 times greater than in those receiving deceased kidney from donor with low log BUN level even after adjusting for potential confounders (HR = 1.06, 95% HR CI = [1.00 - 1.12], *P = 0.0262*). In other words, 6% higher incidence of mortality for patient receiving deceased kidney from donor with high log BUN level compared with those receiving deceased kidney from donor with low log BUN level even after adjusting for potential confounders. However, patient receiving deceased kidney from donor with medium log BUN level appears to be not associated with increase in risk of mortality (HR = 1.01) and this effect did not reach significance after adjusting for potential confounders (*p = 0.4847*). (HR = 1.01, 95% HR CI = [0.96 - 1.07], *p = 0.4847*).

The conclusions were reached that the log of high BUN level of deceased kidney continued to be statistically significantly associated with time to mortality even after adjusting for potential confounders. However, patient receiving deceased kidney from donor with medium log BUN level appears to be not associated with increase in risk of mortality and this effect did not reach significance after adjusting for potential confounders

Based on the results, the conclusions were drawn that the patient with high log BUN level of deceased kidney had statistically significant worse graft and patient survival time compare to patient with low log BUN level of deceased kidney even after adjusting for the

confounding variables. However, not statistically significant differences were seen in graft and patient survival time among patient with medium log BUN level of deceased kidney compare to patient with low after adjusting for confounding variables.

Table 7 and 8 demonstrate univariate and multivariate graft and patient survival analysis using cox regression model.

Table 7
Graft Survival Analysis by Cox Regression Model

Variables	**Graft Survival**		
	Univariate Analysis	**Multivariate Analysis**	
	P	**HR (95% CI)**	***P***
Deceased Donor BUN level (mg/dl)			
< 1.91	-	-	-
1.91 - 2.76	0.0031	1.00 (0.95 - 1.04)	0.9736
> 2.76	< 0.0001	1.08 (1.03 - 1.13)	0.0009
Recipient age groups			
18 - 29 y	-	-	-
30 - 39 y	< 0.0001	0.71 (0.66 - 0.76)	< 0.0001
40 - 49 y	< 0.0001	0.63 (0.59 - 0.67)	< 0.0001
50 - 59 y	0.8562	0.73 (0.69 - 0.77)	< 0.0001
60 - 69 y	< 0.0001	0.94 (0.89 - 1.00)	0.0674
≥ 70 y	< 0.0001	1.23 (1.15 - 1.31)	< 0.0001
Donor age groups			
0 - 17 y	-	-	-
18 - 29 y	0.0001	0.91 (0.86 - 0.96)	<0.0010
30 - 39 y	< 0.0001	1.00 (0,94 - 1.05)	0.9941
40 - 49 y	< 0.0001	1.21 (1.15 - 1.28)	< 0.0001
50 - 59 y	< 0.0001	1.44 (1.37 - 1.51)	< 0.0001
60 - 69 y	< 0.0001	1.71 (1.61 - 1.81)	< 0.0001
≥ 70 y	< 0.0001	1.91 (1.73 - 2.11)	< 0.0001
Recipient gender			
Female	-	-	-
Male	< 0.0001	1.17 (1.14 - 1.20)	< 0.0001

Donor gender			
Female	-	-	-
Male	< 0.0001	0.92 (0.90 - 0.95)	< 0.0001
Recipient race			
White	-	-	-
Black	< 0.0001	1.21 (1.17 - 1.24)	< 0.0001
Hispanic	< 0.0001	0.89 (0.86 - 0.93)	< 0.0001
Other	< 0.0001	0.80 (0.76 - 0.85)	< 0.0001
Donor race			
White	-	-	-
Black	0.0001	1.23 (1.18 - 1.27)	< 0.0001
Hispanic	< 0.0001	1.01 (0.97 - 1.05)	0.5276
Other	0.2800	1.06 (0.99 - 1.14)	0.0712
HCV Sero-status			
Negative	-	-	-
Not done	0.0807	1.04 (0.95 - 1.13)	0.3327
Positive	< 0.0001	1.39 (1.32 - 1.46)	< 0.0001
HBV surface antigen			
Negative	-	-	-
Not done	0.0710	0.95 (0.87 - 1.05)	0.3645
Positive	0.2442	1.06 (0.97 - 1.15)	0.1546
Deceased donor non-heart beating			
No	-	-	-
Yes	< 0.0001	1.05 (1.01 - 1.09)	0.0128
Total serum albumin (g/dl)			
< 3.5	0.8124	1.08 (0.85-1.36)	0.5011
3.5 - 3.99	0.2938	1.00 (0.80-1.26)	0.9514
4.0 - 5.49	0.0048	0.89 (0.70-1.12)	0.3213
> 5.5	-	-	-
Recipient BMI ($kg/m^{2)}$			
BMI < 30	-	-	-
BMI 30-35	< 0.0001	1.10 (1.07 - 1.14)	< 0.0001
BMI 35-40	< 0.0001	1.21 (1.16 - 1.27)	< 0.0001
BMI > 40	< 0.0001	1.41 (1.30 - 1.52)	< 0.0001

Kidney cold ischemic time			
< 16h	-	-	-
16 - 24h	< 0.0001	1.06 (1.3 - 1.09)	< 0.0001
24 - 36h	< 0.0001	1.11 (1.08 - 1.16)	< 0.0001
> 36h	< 0.0001	1.13 (1.05 - 1.20)	0.0003
Kidney received on ice or pump			
Ice	-	-	-
Pump	< 0.0001	0.03(0.99-1.06)	0.0606

Note. Percentages may not equal 100 due to missing data.

Table 7: Graft Survival Analysis by Cox Regression Model

Table 8
Patient Survival Analysis by Cox Regression Model

Variables	**Patient Survival**		
	Univariate Analysis	**Multivariate Analysis**	
	P	**HR (95% CI)**	***P***
Deceased Donor BUN level (mg/dl)			
< 1.91	-	-	-
1.91 - 2.76	< 0.0001	1.01 (0.96 - 1.07)	0.4847
> 2.76	< 0.0001	1.06 (100 - 1.12)	0.0262
Recipient age groups			
18 - 29 y	-	-	-
30 - 39 y	< 0.0001	1.30 (1.13 - 1.49)	0.0001
40 - 49 y	< 0.0001	1.77 (1.56 - 2.00)	< 0.0001
50 - 59 y	< 0.0001	2.83 (2.51 - 3.18)	< 0.0001
60 - 69 y	< 0.0001	4.48 (3.98 - 5.05)	< 0.0001
≥ 70 y	< 0.0001	6.42 (5.68 - 7.26)	< 0.0001
Donor age groups			
0 - 17 y	-	-	-
18 - 29 y	0.8583	0.95 (0.89 - 1.01)	0.1162
30 - 39 y	< 0.0001	1.03 (0.96 - 1.10)	0.3844

40 - 49 y	< 0.0001	1.19 (1.12 - 1.26)	< 0.0001
50 - 59 y	< 0.0001	1.34 (1.26 - 1.42)	< 0.0001
60 - 69 y	< 0.0001	1.56 (1.46 - 1.67)	< 0.0001
≥ 70 y	< 0.0001	1.70 (1.52 - 1.90)	< 0.0001
Recipient gender			
Female	-	-	-
Male	< 0.0001	1.21 (1.18 - 1.25)	< 0.0001
Donor gender			
Female	-	-	-
Male	< 0.0001	0.95 (0.92 - 0.98)	0.0042
Recipient race			
White	-	-	-
Black	0.5631	0.99 (0.96 - 1.02)	0.6953
Hispanic	< 0.0001	0.85 (0.81 - 0.89)	< 0.0001
Other	< 0.0001	0.73 (0.68 - 0.77)	< 0.0001
Donor race			
White	-	-	-
Black	0.0005	1.16 (1.11 - 1.21)	< 0.0001
Hispanic	< 0.0001	1.01 (0.96 - 1.06)	0.5701
Other	0.2469	1.05 (0.97 - 1.14)	0.2085
HCV Sero-status			
Negative	-	-	-
Not done	0.0865	1.00 (0.90 - 1.10)	0.9748
Positive	< 0.0001	1.43 (1.35 - 1.52)	< 0.0001
HBV surface antigen			
Negative	-	-	-
Not done	0.0293	0.93 (0.84 - 1.04)	0.2428
Positive	0.5051	1.04 (0.95 - 1.15)	0.3355
Deceased donor non-heart beating			
No	-	-	-
Yes	0.0946	1.02 (0.97 - 1.07)	0.3057

Total serum albumin (g/dl)			
< 3.5			
3.5 - 3.99	0.0925	1.20 (0.91 - 1.58)	0.1948
4.0 - 5.49	0.4082	1.06 (0.80 - 1.40)	0.6476
> 5.5	0.0705	0.86 (0.65 - 1.14)	0.3128
	-	-	-
Recipient BMI ($kg/m^{2)}$			
BMI < 30	-	-	-
BMI 30-35	< 0.0001	1.08 (1.04 - 1.12)	< 0.0001
BMI 35-40	< 0.0001	1.16 (1.11 - 1.22)	< 0.0001
BMI > 40	< 0.0001	1.31 (1.19 - 1.45)	< 0.0001
Kidney cold ischemic time			
< 16h	-	-	-
16 - 24h	< 0.0001	1.05 (1.02 - 1.09)	0.0018
24 - 36h	< 0.0001	1.09 (1.05 - 1.14)	< 0.0001
> 36h	< 0.0001	1.05 (0.97 - 1.14)	0.1778
Kidney received on ice or pump			
Ice	-	-	-
Pump	< 0.0001	1.06 (1.02 - 1.10)	0.0006

Note. Percentages may not equal 100 due to missing data.

Table 8: Patient Survival Analysis by Cox Regression Model

According to my database, deceased donor causes of death data are shown in figure 10. The primary causes of death among donor were more likely to be head trauma, cerebrovascular/stroke, anoxia, other specify, and CNS tumor; 40.32% (67762), 37.01% (62203), 19.59% (32934), 2.38% (4000), and 0.70% (1180) retrospectively.

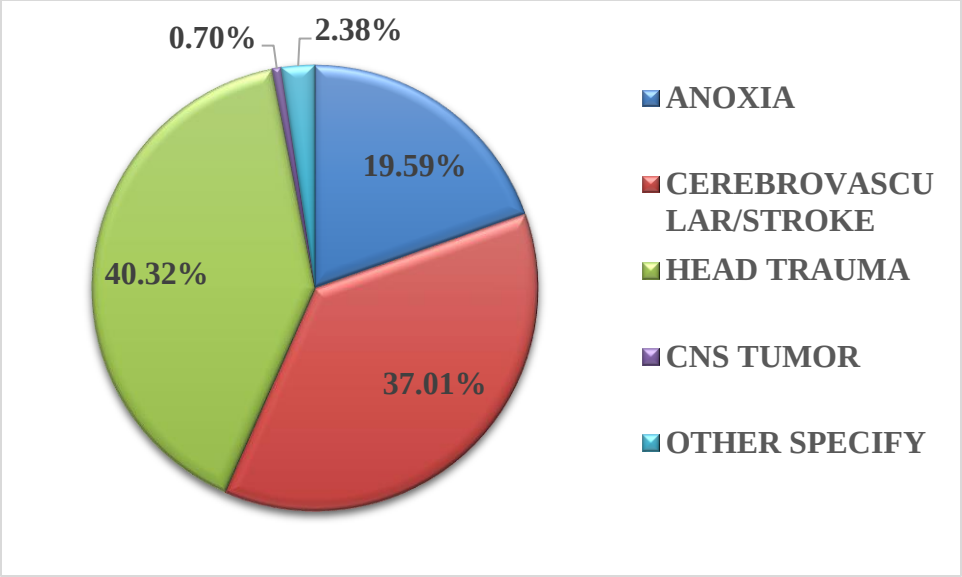

Figure 10: Deceased Donor Cause of Death

Figure 11 illustrates the primary causes of graft failure among recipients. The primary causes of graft failure were more likely to be chronic rejection, other specify, acute rejection, primary failure, recurrent disease, graft thrombosis, infection, BK (Polyoma) virus, urological complications, hyper-acute rejection, then surgical complications, and; 39.93% (14988), 22.89% (8592), 14.43% (5417), 7.03% (2640), 4.68% (1757), 4.61% (1732), 3.17% (1189), 1.76% (662), 0.54% (203), 0.29%(107), and 0.24% (90) respectively.

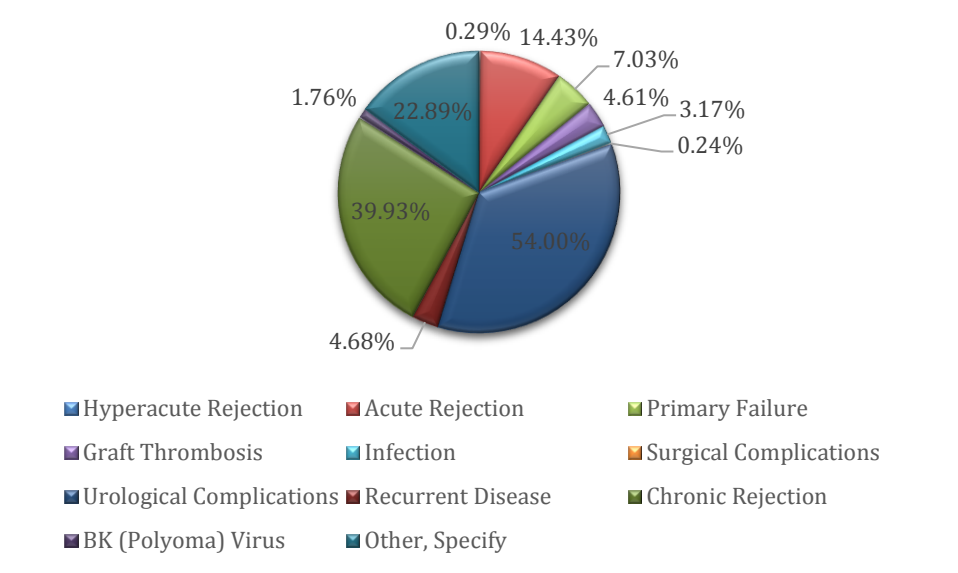

Figure 11: The Primary Causes of Graft Failure among Kidney Recipients

Figure 12 represents the primary cause of recipient death. The primary causes of recipient death were more likely to be unknown, other specify, cardiovascular (myocardial infarction), cardiovascular (other specify) infection (bacterial septicemia), miscellaneous (respiratory failure) malignancy (metastatic other specify) cerebrovascular (stroke), infection (bacterial pneumonia); 29.67% (11400), 14.01% (5382), 11.19% (4299), 7.67% (2949), 6.70% (2574), 3.54%(1360), 3.41% (1310), 2.81% (1080), 2.43% (934) retrospectively.

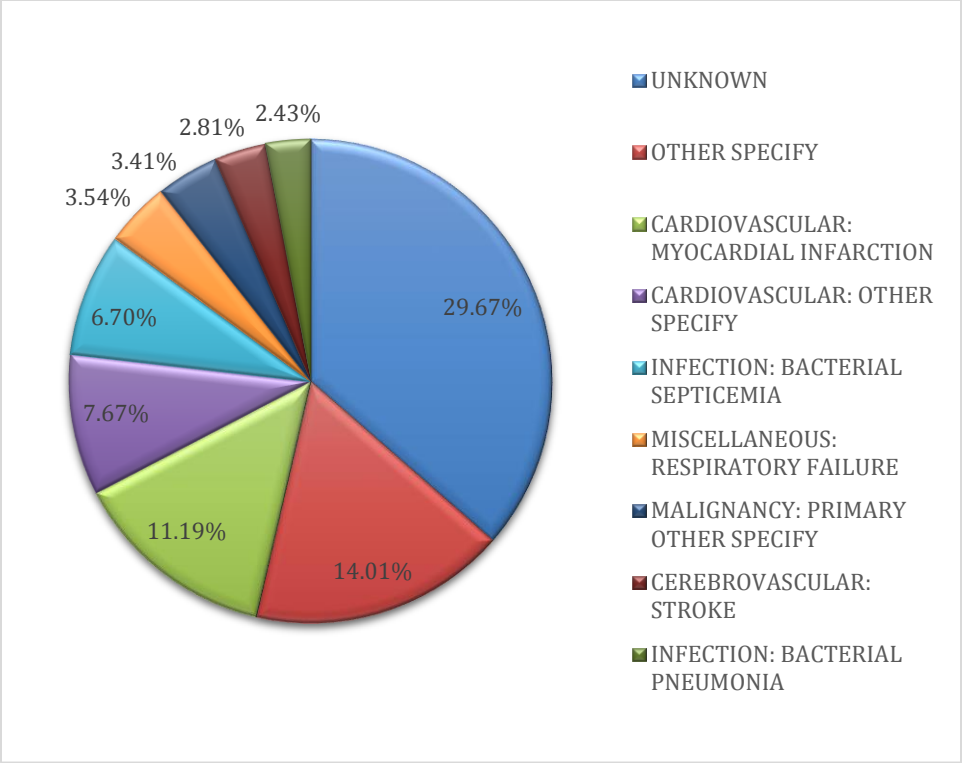

Figure 12: The Primary Cause of Recipient Death

Figure 13 demonstrates the kidney recipients' primary diagnoses at Transplantation. The most common diagnoses were more likely to be hypertensive nephrosclerosis, diabetes mellitus- type II, polycystic kidneys, focal glomerular sclerosis (focal segmental - FSG), other specify, chronic glomerulonephritis unspecified, diabetes - type II non-insulin dependent/adult, malignant hypertension, IGA nephropathy, and systemic lupus erythematosus; 23.42% (38748), 14.82% (24532),9.11% (15082), 5.84% (9664), 4.98% (8246), 4.71% (7790), 4% (6613) ,3.51% (5814), 3.49% (5770), and 3.12% (5170) retrospectively.

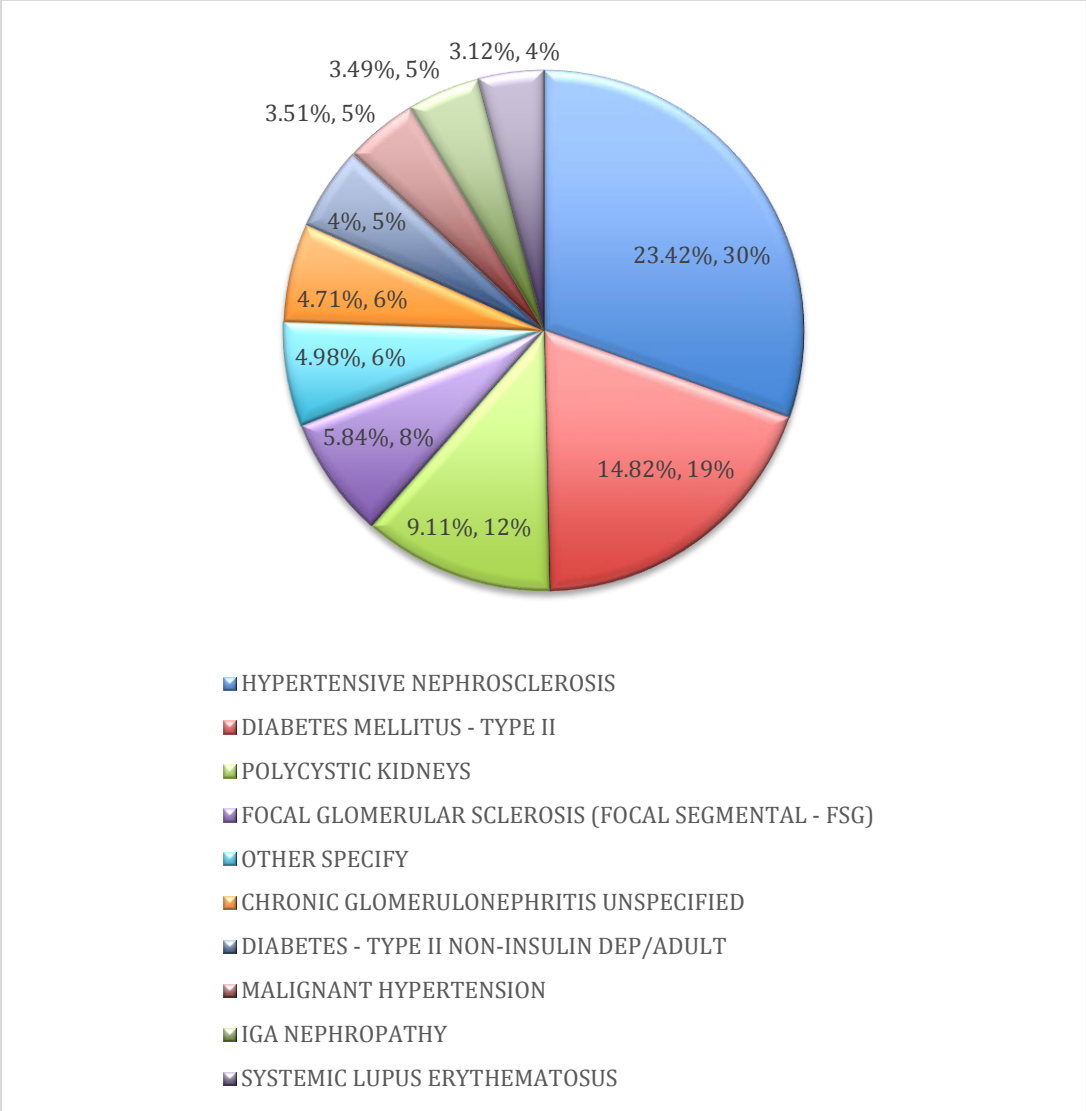

Figure 13: Kidney Recipients Primary Diagnoses at Transplantation

CHAPTER V

DISCUSSION

The aim of the current dissertation is to test the relationship between the blood urea nitrogen (BUN) level of the deceased donor and the survival of the graft and the patient while controlling for such variables as donor and recipient's age, gender and ethnicity as well as recipient's hepatitis C virus (HCV) sero-status, hepatitis B virus (HBV) surface antigen, body mass index (BMI) and total serum albumin. Other variables controlled for include kidney cold ischemic time (CIT), mode of kidney delivery (on ice or pump), and deceased donor's heart beating status (heart beating or non-heart beating) in individuals registered within the United Network for Organ Sharing (UNOS) database. For this purpose, the UNOS dataset was requested and received it. The data were analyzed using Kaplan-Meier and cox regression analysis to identify the relationship between the deceased donor's BUN level and patient and graft survival time. Overall, the findings in this study supported the major hypothesis. This chapter discusses the study results and the limitations of the study.

5.1 Relationship between High Deceased Donor Log BUN Level and Graft Survival Time

High deceased donor blood urea nitrogen (BUN) level is associated with reduced graft survival time. This hypothesis was based on the theory that says high BUN level is associated with poor kidney function [17 18]. Based on this theory, the results of this study

statistically confirm that there is, in fact a relationship between high BUN level of deceased donor and graft survival time.

5.2 Relationship between High Deceased Donor BUN Level and Patient Survival Time

High deceased donor BUN level is associated with low patient survival time. Recipients with high log BUN level of deceased donor displayed lower graft survival and greater risk of death compared with recipients of kidneys from deceased donors with low log BUN level. To confirm high log BUN level of deceased donor as an independent risk factor for graft loss and mortality, statistical model was adjusted for several well-known risk factors as covariates for poor renal transplant outcomes; however, high log BUN level of deceased donor remained independently associated with worse graft and patient survival in multivariate analysis.

To the best of our knowledge of the characteristics that was identified, only the relationship between the recipient's BUN level and graft and patient survival has been previously studied, nevertheless, these the results of these studies are neither consistent nor they indicate a significant influence of the BUN level of the recipient on graft outcomes [17 18]. This scarcity of studies available on recipient's BUN affecting the outcomes of graft and patient survival motivated investigations about other predictors that might influence the outcome of kidney transplantation, specifically graft and patient survival. Therefore, examining the role of the BUN levels of recipients and donors was highly recommended, but data regarding the effect of donor's BUN level on kidney transplantation outcome was lacking. Thus, this study was designed to examine the difference in graft and patient survival rate between three groups (high, low and medium

deceased donor's BUN level).

To our knowledge, this is the largest national study to examine the effects of log deceased kidney donor BUN level on the outcomes of kidney transplantation- graft and patient survival time. It showed that high log BUN level of deceased donor was an independent risk factor for graft loss and patient death in kidney transplant patients while controlling for other variables such as donor and recipient's age, gender and ethnicity as well as recipient's hepatitis C virus (HCV) sero-status, hepatitis B virus (HBV) surface antigen, body mass index (BMI) and total serum albumin. Other variables controlled for include kidney cold ischemic time (CIT), mode of kidney delivery (on ice or pump), and deceased donor's heart beating status (heart beating or non-heart beating).

High log BUN level of deceased donor was associated with worse graft and patient survival was hypothesized, but prospective studies need to be performed to assess a causal association between such variables. In our study, Kaplan-Meier analysis revealed that graft and patient survival were significantly affected by deceased donor BUN level ($P < .0001$). This was done using unadjusted and adjusted analysis for both graft survival and patient survival using the cox regression model.

In unadjusted analysis of graft survival, for example, the patients receiving deceased kidney donor with high BUN level had 12% higher risk of graft failure compared with those receiving deceased kidney donors with low BUN level (HR = 1.122, 95% CI = [1.095 - 1.149], $P < 0.0001$). Patients receiving deceased kidneys from donors with medium log BUN levels had 3% higher risk of graft failure compared with those receiving deceased kidneys from donors with low log BUN levels (HR = 1.035, 95% CI = [1.012 - 1.059], $P = 0.0031$).

In unadjusted analysis of patient survival, patients receiving deceased kidney donors with high BUN levels had 15% higher risk of death compared with those receiving kidneys from deceased donors with low BUN levels (HR = 1.152, 95% CI = [1.121 - 1.183], *P < 0.0001*). Patients receiving deceased kidneys from donors with medium log BUN levels had 6% higher risk of mortality compared with those receiving deceased kidneys from donors with low log BUN levels (HR = 1.067, 95% CI = [1.041 - 1.094], *P < 0.0001*).

In our adjusted multivariable cox regression analysis model, high log BUN level of deceased donor remained an independent predictor of graft loss and patient death compared to low log BUN level of deceased donor (hazard ratio [HR], 1.080; 95% hazard ratio confidence limits [CI], 1.032 - 1.131; *P = 0.0009*) and (hazard ratio [HR], 1.063; 95% hazard ratio confidence limits [CI], 1.007 - 1.121; *P = 0.0262*), respectively. In contrast, medium log BUN level of deceased donor was not independently associated with graft loss and patient death.

To reiterate, this study demonstrated that recipients with high log BUN level of deceased donor had lower graft and patient survival time compared to recipients with low log BUN level of deceased donors. There is no statistically significant difference in graft and patient survival time were shown among patients with medium log BUN level of deceased kidney compared to patients with low log deceased donor BUN level after adjusting for confounding variables. This might because BUN level has more negative effect on survival at higher level. This result can provide an explanation as to why some kidney grafts are lost earlier than others while other graft and patient factors are the same.

In addition, our study indicated that high log deceased donor BUN level was independently associated with increased graft failure and patient mortality.

Our findings can potentially help allocate resources to donors with more favorable BUN levels rather than using the resources on donors that are less likely to produce favorable patient and graft survival.

Our study has several limitations. Some of them are common to all retrospective database analyses of registry data including selection bias, misclassification error, and/or missing values. There were several potentially relevant covariates that could not be included due to the lack of data. The most important of them were the BUN level of the recipient and the BUN level of the living donor. Therefore, our findings may not apply to recipients of kidneys from living donors. However, the large sample size was a strong attribute of the study compared with single centered databases.

CHAPTER VI

SUMMARY AND CONCLUSION

SUMMARY

The purpose of this dissertation was to examine the relationship between the BUN level of the deceased donor and the survival of the graft and the patient while controlling for such variables as donor and recipient's age, gender and ethnicity as well as recipient's hepatitis C virus (HCV) sero-status, hepatitis B virus (HBV) surface antigen, body mass index (BMI) and total serum albumin. Other variables controlled for involve kidney cold ischemic time (CIT), mode of kidney delivery (on ice or pump), and deceased donor's heart beating status (heart beating or non-heart beating) using the most updated data from the United Network for Organ Sharing (UNOS) dataset. Our specific objective was to run a statistical analysis on the UNOS dataset to see if there was a significant relationship between deceased donor's BUN level and patient and graft survival while adjusting for all other confounding variables in the United States between 1987 and 2016. To accomplish these goals and objectives, the UNOS dataset was employed, selected the variables of interest and decided on how to measure variables to see what type of statistical relationship existed between the variables. Data from the UNOS database, which included the information about the donors (both living and deceased) and recipients of renal transplantations, reported to the Organ Procurement and Transplantation Network (OPTN) since October 1st 1987. Each record in the database corresponds to one transplant or waitlist registration case and includes the most recent data such as the patient and graft survival.

Each follow up is documented through one record, thus creating multiple records per transplant. To protect patient and center privacy, only patient ID number is used, while any identifier information about patient or center is excluded. The dataset used for the current study was gathered between October 1987 and March 2016. The sample size for our study consisted of a total of 168,081 adult primary kidneys only transplantations from deceased kidney donors.

KEY FINDINGS

- Preliminary results indicated that deceased donor's BUN level might predict patient and graft survival time. In patients registered in the UNOS database, those with high deceased donor BUN levels had the lowest mean patient and graft survival time, while patients with low deceased donor BUN levels had higher mean patient and graft survival time that was statistically significant ($P < 0.0001$).
- The results of this study concluded that patients with high BUN level of deceased kidney donor had the lowest graft and patient survival time compared to patients with low BUN levels of deceased kidney; (HR = 1.080; 95% hazard ratio CI = [1.032 - 1.131], $P = 0.0009$) and (HR = 1.063, 95% hazard ratio CI = [1.007 - 1.121], $P = 0.0262$) retrospectively. There were no significant differences in graft and patient survival time among patients with medium BUN levels of deceased kidney donors compared to patients with low donor BUN levels after adjusting for confounding variables; (HR = 1.001, 95% CI = [0.958 - 1.045], $p = 0.9736$) and (HR = 1.018, 95% CI = [0.968 - 1.072], $p = 0.4847$) retrospectively.

CONCLUSION

Our study indicates that the patient with high log BUN level of deceased kidney (> 2.79 mg/dl) had worst graft and patient survival time compare to patient with low log BUN level of deceased kidney. In addition, it is independently associated with worse graft and patient survival time compared to low log BUN level of deceased donor, and it may influence the graft and patient survival in certain subsets of patients with kidneys from deceased donors. However, there were no significant differences in graft and patient survival time among patient with medium log BUN level of deceased kidney compare to patient with low after adjusting for confounding variables.

It is to noted that White, Black and Hispanic donors' races have significant differences at 5 year graft and patient survival time while donors of other races (Asian, American Indian/Alaska native, Native Hawaiian/other Pacific Islander, and multiracial) did not show any significant differences due to genetic influences.

The probability of graft and patient survival of recipient with high log deceased donor BUN level was lower at 5 years, 10 years, 15 year, 20, year and 22 year compare to those with medium and low log deceased donor BUN level.

These results can potentially contribute to a more efficient allocation of resources to donor sources with better outcome prospect.

RECOMMENDATIONS

1. Further studies are required to establish a causal relationship and to assess the discussed relationship in other kidney transplantation populations.
2. The UNOS data does not provide information about living donor BUN level. Including this variable and its influence on graft outcomes will help improve the long-term outcome of kidney transplantation.
3. The role of genetic vs. environment should be further clarified in future research.
4. Since BUN levels can be affected by other factors such as protein intake, muscle mass, dehydration, and plasma volume, future research should control for these variables.

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