THE IMPACT OF DELAYED GRAFT FUNCION ON PATIENTS AND GRAFT SURVIVAL IN CADAVERIC KIDNEY TRANSPLANT RECIPIENTS AT SIRIRAJ HOSPITAL, THAILAND

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ABSTRACT

Delayed graft function (DGF) is one of the most important complications in the post-transplant period, because it has an adverse effect on both immediate and long-term graft survival. This study aimed at examining possible risk factors including the recipient's age, gender, and time of dialysis; the donor's age and gender; and other transplant factors including cold ischemia time (CIT), human leukocyte antigen (HLA) matching, panel reactive antibody (PRA), and induction therapy using the immunosuppressant IL-2 and their association with delayed graft function (DGF) and graft survival. Data was collected from 140 cadaveric kidney transplants at Siriraj Medical School Hospital, Bangkok, Thailand between January 2002-January 2009.

Univariate and multivariate analysis, based on the140 cadaveric recipients, indicated that the duration of dialysis was significantly associated with DGF (OR= 4.167, 10.47; 95%CI=1.260-13.83, 1.93-56.74; p =0.020, 006), respectively. Older donors (age $\geq$ 50 years) and among all causes of death, cerebral vascular accidents (CVA), were associated with DGF (OR=1.43, 3.883; 1.77, 0.72) respectively, but not significant.

The incidence of DGF in this study was 80.7 %. The graft survival function rate was significantly different between grafts with DGF and those with immediate graft function (IGF) after 7 years of follow-up with rates of 56.3 % and 89% (p=0.016), respectively. The other factors indicated no significant difference between grafts with DGF and those with IGF.

The number of patients displaying DGF who were associated with the transplant factors of CIT <24 hours, CIT $\geq$ 24 hours, HLA < 3 mismatch, HLA $\geq$ 3 mismatch, PRA < 30%, PRA$\geq$ 30%, receiving induction therapy, and not receiving induction therapy were76 (79.2%), 29 (85.3%), 50 (78.1%), 51 (81%), 101(81.5%), 12 (75%), 38 (84.4%) and 75 (78.9%), respectively. These factors were associated with DGF but not significant.

The data suggests that DGF is critical to the survival of the grafts and patients. The prevention and reduction of causes associated with DGF could increase the success of kidney transplants.

KEY WORDS : DELAYED GRAFT FUNCTION/ IMMEDIATE GRAFT FUNCTION/CADAVERIC DONOR/ GRAFT SURVIVAL/ PATIENT SURVIVAL

72 pages

ผลกระทบของภาวะไตทำงานล่าช้าต่อภาวะรอดชีพของผู้ป่วยและไตที่ได้รับการปลูกถ่ายในผู้ป่วยที่ได้รับการผ่าตัดปลูกถ่ายไตจากผู้บริจาคที่เสียชีวิตด้วยภาวะสมองตายที่โรงพยาบาลศิริราช, ประเทศไทย

THE IMPACT OF DELAYED GRAFT FUNCTION ON PATIENTS AND GRAFT SURVIVAL IN CADAVERIC KIDNEY TRANSPLANT RECIPIENTS AT SIRIRAJ HOSPITAL, THAILAND

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บทคัดย่อ

ภาวะไตทำงานล่าช้าเป็นภาวะแทรกซ้อนภายหลังการผ่าตัดเปลี่ยนไตที่สำคัญ ซึ่งส่งผลกระทบต่อไตใหม่ที่ได้รับทั้งทันทีภายหลังการผ่าตัด และระยะยาว การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อทำการศึกษาปัจจัยเสี่ยงที่มีความสัมพันธ์ต่อการเกิดภาวะไตทำงานล่าช้า และระยะเวลาที่ไตทำงานภายหลังการผ่าตัด

โดยทำการศึกษาแบบย้อนหลัง ในผู้ป่วยที่ได้รับการผ่าตัดปลูกถ่ายตัดจากผู้บริจาคที่เสียชีวิตจากภาวะสมองตายของโรงพยาบาลศิริราชในช่วงเดือนมกราคม 2545 ถึง มกราคม 2552 จำนวน 140 ราย ที่มีภาวะไตทำงานล่าช้าภายหลังการผ่าตัด และศึกษาปัจจัยที่ส่งผลกระทบต่อการเกิดภาวะไตทำงานล่าช้า โดยศึกษาปัจจัย 3 ด้านได้แก่ ปัจจัยของผู้รับบริจาค (อายุ ,เพศ และ ระยะเวลาฟอกเลือด) , ปัจจัยผู้บริจาค (เพศ, อายุและสาเหตุการเสียชีวิต) ปัจจัยในส่วนของ transplant factors (PRA, HLA,CIT และการได้รับ ยาในกลุ่ม IL-2 ก่อนการผ่าตัด)

จากการวิเคราะห์ข้อมูลเชิงซ้อนโดยการวิเคราะห์ถดถอยเชิงพหุแบบลอจิสติก พบว่าระยะเวลาฟอกเลือดก่อนได้รับการผ่าตัดที่ มากกว่า 24 เดือน มีความสัมพันธ์ต่อการเกิดภาวะไตทำงานล่าช้าอย่างมีนัยสำคัญทางสถิติ

(OR= 4.167vs10.47, 95%CI=1.260-13.83vs1.93-56.74, p =0.020vs.006). ในด้านของผู้บริจาคนั้น ผู้บริจาคที่มีอายุมากกว่าหรือเท่ากับ 50 ปี สาเหตุของการเสียชีวิต จาก CVA มีความสัมพันธ์ต่อการเกิดภาวะไตทำงานล่าช้าแต่ไม่มีนัยสำคัญทางสถิติ สำหรับปัจจัยอื่น ๆนั้นไม่มีนัยสำคัญทางสถิติ

อัตราการเกิดภาวะไตทำงานล่าช้าภายหลังการผ่าตัดคือ 80.7 % โดยอัตราการทำงานของไตภายหลังการผ่าตัดถึงสิ้นสุดการศึกษาที่ 7 ปี ในกลุ่ม DGF และ IGF คือ 56.3 % และ 89 % ซึ่งแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p-value = 0.016) , ปัจจัยอื่น ๆ ได้แก่ CIT < 24 ชั่วโมง และ ≥ 24 ชั่วโมง 76ราย (79.2%), 29ราย (85.3%), HLA < 3 mismatch 50ราย (78.1%), HLA ≥ 3 mismatch 51 ราย (81%), PRA < 30% 101ราย (81.5%), PRA≥ 30% 12ราย (75%) และจำนวนผู้ป่วยที่ได้รับและไม่ได้รับ induction therapy 38 ราย (84.4%) และ 75ราย (78.9%)ไม่มีความสัมพันธ์ต่ออัตราการทำงานของไตภายหลังการผ่าตัด

ภาวะ DGF มีผลต่ออัตราการทำงานของไตในระยะยาว การป้องกัน หรือ ลดสาเหตุของการเกิดภาวะ DGF จะมีประโยชน์อย่างมากต่อการผ่าตัดเปลี่ยนอวัยวะ

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Abbreviation or symbol	Term
ESRD	end-stage renal disease
ECDs	expanded criteria donors or marginal donors
SGF	slow graft function
DGF	delayed graft function
GNF	graft non function
IGF	immediated graft function
ATN	acute tubular necrosis
AMR	antibody mediated rejection

CHAPTER I
INTRODUCTION

1.1 Rationale and Background

Kidney is an essential organ in the human body. The main function of kidney is to maintain body fluid by excreting wastes, concentrating urine, and then regulating electrolytes. The malfunction of kidney is directly affected human life. One of diseases causing the failure of kidney function is end-stage kidney disease or end-stage renal disease (ESRD) which results in complete or nearly complete the failure of kidney function considering as life threatening disease.

The causes of ESRD are directly from diabetes and high blood pressure resulting in chronic glomerulonephritis and diabetic nephropathy. Additionally, ESRD are indirectly caused by inborned disease, the side effect of medicines and injuries. The estimated incidence of ESRD in Thailand is approximately 50 per a million populations. Of 65 millions of Thai population, there will be almost 7,000 ESRD patients who are receiving dialysis treatment, either hemodialysis or continuous ambulatory peritoneal dialysis (2).

Based on the medical practices, two effective treatments of ESRD are dialysis and kidney transplantation. The dialysis assists the body to remove waste substances and eliminate excess fluid from the blood. It can replace the function of kidneys. The dialysis may also be used for individual patient who is exposed or ingested toxic substances to prevent renal failure. The typical dialyses used are either peritoneal dialysis or hemodialysis. These two methods use the special medical device functioning as a kidney to filtrate the waste fluid out of the blood. The difference between two methods of dialysis is where the surgically a soft tube placed into the body. The peritoneal dialysis is performed at the lower abdomen while hemodialysis is at the patient's arm. It can be performed three to five times a day during the body wakes up. The hemodialysis is usually performed several times a week and each time

lasts four to five hours. The method has received much attention due to the ease of practice and convenience. The data from the United States reported that more than 400,000 people are on long-term dialysis and more than 20,000 have already been kidney transplanted. According to the data in 1999, more than 4,400 patients received hemodialysis in the department of veterans affairs (VA), USA with the estimate cost of over $60 million.

The alternative effective medical treatment for ESRD is the kidney transplantation. Two different types of transplantation commonly performed in medical operation are living and cadaveric kidney transplantation. The patient on living kidney transplantation will receive the kidneys either from family related donors or non family related donors. Both of these donors must be still alive while the kidneys are transplanted. The family related donors can be categorized into two groups that are the first and the second degree. The first group of family related focuses on parents, children, and siblings having at least one-haplotype match. The second group belongs to cousins, uncles, aunts. The patients could also receive the kidneys from non family related donors including spouses, friends, strangers and donors of paired-kidney exchange program. Of these two types of donors, the family related donors could potentially be benefit to the patient due to a high percentage of biologically matching blood. Besides the living kidney transplantation, the cadaveric kidney transplantation is also a method of choice for transplantation due to the donor scarcity. The cadaveric donor or brain death cadaver has two difference types which are expanded criteria donors or marginal donors (ECDs) and non-expanded donors. The ECDs are defined by the United Network for Organ Sharing (UNOS), USA as “those donors have been demonstrated to increase the risk of late allograft loss because of certain clinical characteristics”. The UNOS renal transplant using a total of 122,175 registered patients who were on the waiting list during 1992 to 1997 (3). Based on the data of UNOS, since November 2006, the patients have accounted on the waiting list more than 100,000 candidates. Out of these numbers, 70,000 patients are awaiting for kidney transplantation (3). Unfortunately, a number of patients on the waiting list continue to grow disproportionate to a number of organ donors for transplantation.

In order to cure the kidney disease, especially ESRD either by dialysis or kidney transplantation, a number of survival rates and medical cost must be taken into account. Ojo et al (4) examined the effect of ECD kidneys on survival recipients compared to those numbers on the waiting list. On the average, patients with marginal kidney transplantation could live 5 years longer than the transplanted patients who remained on dialysis. A number of factors affected survival rate of ECD transplanted patients are causes of ESRD, recipient age, and race. Compared between two types of transplantation, the cadaveric transplanted recipients could ideally extend their life for another 13 years. Patient survival after renal transplantation varies based upon several factors such as sources of the allograft, patient age, the presence and degree of severity of comorbid conditions. Other possible contributing factors include gender, race, and degree of immunosuppression. However, over the last decade these survival rates have slightly increased, particularly among diabetic and deceased donor transplant recipients. These could be the results from the improvement of renal allograft function within one year, the effective management of intercurrent disorders, and a lower rate of death from infections (5).

In terms of medical costs and clinical outcomes, the results showed that the kidney transplantation had lower in medical expenses (6) with better long term clinical outcomes (5) than dialysis. Therefore, the kidney transplantation remains the treatment of choice for patients with end-stage renal disease in terms of quality of life and life expectancy (1).

Although the kidney transplantation could be a better choice for ESRD than dialysis, the most common clinical complications of renal transplantation are allograft dysfunction cadaver and in some cases, the manifestation of early dysfunction of transplanted live kidney leading to the clinical syndrome called delayed graft function (DGF). DGF is a form of acute renal failure that results in post-transplantation oliguria leading to graft loss in some cases. In the rare cases, the graft had never functioned properly. Though, it is generally accepted that not all kidneys for transplantation are similar. The differences are from the source of donors who are alive or deceased. The data have showed that the survival of patients receiving an allograft from a living donor is superior to those who receive a kidney from a deceased

donor, including both non-extended criteria and extended criteria donors (7, 8). The statistically data of recipients receiving a living donor kidney had the survival rates of 98% and 91% during one and five years post-transplantation. The survival rates for those who received the kidney from a deceased non-extended criteria donor transplant and those who received the kidney from a deceased extended criteria donor transplant were 96% and 84%, 91%, and 69% during one and five years post-transplantation, respectively.

The data from the United States reported that within one year the renal allograft cases found approximately 92% for a non-extended criteria deceased donor kidney and 96% for a living kidney donor (9). The organ procurement and transplantation network database in USA showed the cases of DGF vary enormously from 2 % to 50 % (10) in cadaveric donor kidney transplants and 4 % to 10 %, average 5 % in living donor kidney transplants (11).

After the kidney transplantation, the first postoperative week is generally characterized by progressive improvement in the overall condition of the patients in conjunction with the steady improvement of kidney function. The management of the transplanted recipient during the first week is largely determined by the quality of function of the allograft. Patients typically exhibit one of three patterns of function: excellent graft function, slow graft function (SGF), or delayed graft function (DGF).

The clinical problems have found in the patients with slow graft function or moderate graft dysfunction considered as nonoliguric and the declined in serum creatinine levels by < 20% in the first 24 hours posttranplant (Hassanain et al. 2009). These patients do not have to perform dialysis within the first postoperative week, even though the kidneys still not function properly. Slow graft function is a milder form of DGF which has similar pathophysiology and clinical significance (12).

If the incidence of DGF occurs, there is a need for dialysis during the first week after kidney transplantation, although the degree of renal damage could not be measured (13). The conditions considered as DGF include early urine output of <1200 mL/d or no decrease of 10% of serum creatinine or high serum creatinine level during the first 48 hours after transplantation (14). However, in this study the condition of

DGF covers the need of dialysis during the first week after kidney transplantation or serum creatinine < 30% within 48 hr or urine output < 1000 ml/day and no dialysis. DGF is associated with the risk of both short-term and long-term graft loss (15). The major causes of DGF which profoundly impact on graft survival are postischemic acute tubular necrosis (ATN), hyperacute and acute antibody mediated rejection (AMR), accelerated rejection superimposed on ischemic (ATN), the obstruction of urinary tract due to ureteral necrosis with a urinary leak or hematoma and atheroemboli or thrombosis of the renal artery or vein (16, 17).

Four variables associated with the increased risk of DGF are donor, recipient or patient, procurement or preservation and body immunity. For the donor, the risk conditions include age over 50 years old, gender (female to male), cadaver or brain-death cause of death (CVA > trauma), ethnicity (African to American), cold ischemia time (>12 hours), creatinine clearance (<100 ml/min), biopsy for vascular atherosclerosis, living versus cadaveric donor, hypotension, inotropic support and increased serum creatinine level. The recipient factors cover age over 55 years old, gender (female to male), ethnicity (African-American), BMI, perioperative hemodynamics, extracellular fluid volume status, primary disease such as diabetes, preoperative mode of dialysis (HD > PD), history blood transfusion, duration on dialysis before transplantation and increased thrombosis risk such as Factor v Leider mutation. The considerations of procurement or preservation include an inadequate flushing and cooling condition, type and quantity of flushing solution, traction on renal vessels, cold and warm ischemia time. The immunology has to be performed as followed: HLA match / mismatch (>1 mismatch), panel reactive antibody titer (PRA > 50%) and positive cross match. The improvement of clinical outcomes after renal transplantation involve better comprehension of the rejection response, the improved preservation technique of organs, the judicious use of cyclosporine or tacrolimus and the application of anti-lymphocyte agents for the prevention and treatment of rejection (18).

Recently, Thailand have performed the kidney transplantation from living related donor, living unrelated donor and cadaveric donor by the Organ Donation Center of the Thai Red Cross Society which acts as the center for organ donation and

allocation of cadaveric kidneys. Organs are shared among patients on a national waiting list based on HLA matching, anti-HLA antibody titers, and waiting time. However, the hospital that procures the donor has the right to use one of the kidneys for the best HLA-matched patient on its list.

Due to the insufficient numbers of kidney from healthy living donors for transplantation and a large number of patients waiting for operation, a cadaveric kidney donor is considered as an important resource for saving patient's life. Therefore, there is a need to investigate the risk factors affecting transplantation including recipient, donor and operation. The results of this study focusing on the delayed graft function rate, the graft survival rate and the impact of DGF on short- and long-term outcome of transplantation could deliver significantly benefits to kidney transplantation.

1.2 Research Questions

1. What is the delayed graft function rate on cadaveric kidney transplant recipients at Siriraj Medical School Hospital?
2. What are the impacts of Delayed graft function on patients?
3. What is the graft survival rate among DGF and non DGF?

1.3 Research Objectives

1. To evaluate the delayed graft function rate on cadaveric kidney Transplant recipients at Siriraj Medical School Hospital.
2. To evaluate the risk factors are impacts of Delayed graft function (DGF) after cadaveric kidney transplantion
3. To compare the graft survival rate in DGF and non DGF after cadaveric kidney transplantation.

1.4 Research Hypothesis

Are there any significant differences of graft survival rate between DGF and non-DGF?

Null hypothesis or Ho:

graft survival rate of DGF = graft survival rate of non DGF

Alternative Hypothesis or Ha :

graft survival rate of DGF $\neq$ graft survival rate of non-DGF

1.5 Scope and Limitation

All medical records of the all consecutive patients who undertook kidney transplantation at Siriraj Medical School Hospital, Mahidol University from January, 2002 to January, 2009 were screened. The study was focused only on cadaveric donor. The demographic data of patients and donors was collected. The impacts of delayed graft function on patients were examined. The rates of delayed graft function and graft survival were analyzed.

Definitions

The Transplant Operation

The Kidney transplantation is a surgical procedure to remove a healthy, functioning kidney from a living or brain-dead donor and implant it into a patient with nonfunctioning kidneys.

In adults, the renal graft is placed extraperitoneally in the iliac fossa through an oblique lower-abdominal incision; in small children, it is placed retroperitoneally through a midline abdominal incision. The renal arterh is anastomosed end-to-end to the recipient's hypogastric artery or end-to-side to the common iliac artery. Renal artery thrombosis, a rare event but serious complication, occurs more frequently with an end-to-end than with an end-to-side anastomosis. The renal vein is anastomosed to the iliac vein in adults and to the inferior vena cava in children. The donor ureter is inserted by creating a submucosal tunnel in the recipient's lymphatic ducts, from the renal hilum, or both. Symptomatic lymphoceles

(in which there is obstruction of the ureter or the venous drainage) are relieved by percutaneous aspiration, drainage into the peritoneal cavity, or both (12).

Cadaver kidney donor.

The kidney from donor are brain-dead cadavers whose hearts are still beating; these are often victims of head trauma, vascular catastrophes, cerebral anoxia, and nonmetastasizing brain tumors.

Over 50 percent of kidneys and most of the extrarenal solid organs that are transplanted are recovered from deceased donors.

Marginal donor or expanded criteria donors (ECDs).

This study we use the marginal donor or expanded criteria donors (ECDs) are defined by UNOS. These donor characteristics are age greater than 50 years, long-standing history of HTN, cerebral vascular accident (CVA) as the cause of death, terminal serum creatinine greater than 1.5 mg/dL, diabetes, or long CIT (72).

Donor age

Previously, older donors, such as those over 50 years of age, were not considered suitable. However, the kidneys from such donors are now commonly used if these individuals are in good physical and mental condition and have adequate kidney function.

The increased use of older donors was reflected in a 2007 survey of kidney transplant centers in the United States in which almost 60 percent of centers had no upper age limit for kidney donors (65). Among the remaining centers, an age limit of 75, 70, 65, 60, and 55 years was reported in 4, 5, 21, 7, and 1 percent, respectively. With respect to a lower age limit, most centers report that an age less than 18 years is an absolute exclusion criterion. In the 2007 survey (65), for this study we excluded prospective donors less than 18 years of age.

Cold ischemia time (CIT).

Cold ischemia time (CIT) is associated with delayed graft function (DGF) and transplant outcome. Several strategies to reduce CIT have been proposed. We defined CIT as the time from removal of the kidney from cold storage or perfusion with preservation solution in the donor to completion of the renal arterial anastomosis (66).

The human leukocyte antigen (HLA).

HLA system is synonymous with the human major histocompatibility complex (MHC). These terms describe a group of genes on chromosome 6 that encode a variety of cell surface markers, antigen-presenting molecules, and other proteins involved in immune function.

Delayed Graft Function (DGF)

DGF is a form of acute renal failure resulting in post-transplantation oliguria, increased allograft immunogenicity and risk of acute rejection episodes, and decreased long-term survival. (57)

We propose to define DGF in clinical studies retrospectively on the basis of renal function, distinct from the need of dialysis treatment. Using the absence of a spontaneous decrease of serum creatinine of more than 10% per day for at least 3 consecutive days within 1 week after transplantation, excluding acute rejection, and calcineurin inhibitor toxicity as a possible cause of this DGF.

DGF is defined as the need of dialysis treatment in the first week after renal transplantation and exclude other reasons, like hyperkalemia and/or fluid overload. We include slow graft function (SGF).Because SGF is similar in term of pathogenesis but differ in degree. SGF is defined as Scr. < 30% within 48 h or urine output < 1000 ml/day, no dialysis.

Survival time.

We define as the time at first date of transplantation until the end of the studied or the time that serum creatinine rising more than 2 mg/dl

CHAPTER II
LITERATURE REVIEW

2.1 General Background of Kidney transplantation

Kidney transplantation is an effective medical treatment for end-stage kidney disease or end-stage renal disease (ESRD). ERSD is considered as a serious illness that is potentially caused death within a short period of time. The kidney transplantation is a surgical procedure to remove a healthy, functioning kidney from a living or brain-dead donor and then implant it into a patient with nonfunctioning kidneys. In adults, the renal graft is placed extraperitoneally in the iliac fossa through an oblique lower-abdominal incision. In small children, it is placed retroperitoneally through a midline abdominal incision. The renal artery is anastomosed end-to-end to the recipient's hypogastric artery or end-to-side to the common iliac artery. Renal artery thrombosis, a rare event but serious complication, occurs more frequently with an end-to-end than with an end-to-side anastomosis. The renal vein is anastomosed to the iliac vein in adults and to the inferior vena cava in children. The donor ureter is inserted by creating a submucosal tunnel from the renal hilum. Symptomatic lymphoceles caused by the obstruction of the ureter or the venous drainage are relieved by percutaneous aspiration or drainage into the peritoneal cavity (19).

The decision to initiate the kidney transplantation in a patient with end-stage renal disease involves the consideration of subjective and objective parameters of the physician and the patient. These parameters are often modulated by the patient's perception of his or her quality of life (20). The first renal transplant in Thailand was performed on March 3, 1972 at the King Chulalongkorn Memorial Hospital in Bangkok. The second successful cadaveric renal transplant was performed at the Siriraj Medical School Hospital in 1973. Only Chulalongkorn Hospital and Siriraj Medical School Hospital have been carrying on kidney transplantations, in average of less than 20 cases a year, up to 1984 (21, 22).

The kidney used for transplantation can be obtained from two different types of donors. One is a living donor and the other is a cadaveric donor. Living donors is divided into living related donors who are either the first degree relative (for example parents, children, and siblings) with whom at least one-haplotype is matched or the second degree relative (for example, cousins, uncles and aunts) and living unrelated donors who could be spouses, friends, or strangers who are willing to donate the kidney. Based on medical evidences of Okamoto et al.(2009) who studied short and long term donor outcomes after kidney donation at Japanese single center between 1970 and 2006, the total number of collected donors were 601 donors. It was reported that 481 donors (80%) were available at the time of inspection. Of 481 donors, a number of survival donors were 426 donors (88.5%). The survival rate of living donor at 5, 10, 20 and 30 years were 98.3%, 94.7%, 86.4%, and 66.2%, respectively. As a result, living donors is a key factor to prolong patient lives with less impact on donor lives themselves.

Due to that fact that the living donor is a very scarcely resource, therefore, the brain death or cadaveric donor is also needed for transplantation, or called as cadaveric kidney transplantation. Most of the brain death may from head trauma, vascular catastrophes, cerebral anoxia, and nonmetastasizing brain tumors. Cadaver solid organ transplantation requires that the organ transplants must be in a state of good function until the moment of harvest. Over 50 percent of kidneys and most of the extrarenal solid organs that are transplanted are recovered from deceased donors. At Siriraj Medical School Hospital, most of cadaveric kidney has been donated from the Organ Donation Center of Thai Red Cross Society. Regarding to medical ethics, societal acceptance and the legal and medical establishments of brain death criteria are essential for cadaveric kidney transplantation. At present, there are many centers carrying kidney transplant. In Thailand, the donation of kidney can legally be from only living related donor, spouses, and cadaveric donors. The criteria of brain death donor have been officially announced by the Thailand Medical Association since 1989. Owing to a large number of patients on the waiting list, the kidney organs are shared based on HLA matching anti-HLA antibody titers and waiting time. However, if the hospital could select the best HLA matching for its own procured patients on the local list (2).

2.2 Complications associated with renal transplants

The successful outcome of transplantation is the recovery of renal function. However, the common complications found in patients with renal transplants vary from graft non function (GNF), slow graft function (SGF), immediate graft function (IGF), oliguria, and delayed graft function (DGF) (Walele et al. 2002). The primary non-function of the allograft refers to a graft that never recovers renal function. SGF is a post-transplant renal failure without the need for dialysis. SGF and DGF are similar in terms of pathogenesis but differ in degree. SGF is clinically defined as serum creatinine < 3 mg/dl by post-operative day no. 5 and no dialysis (Humar et al. 2002). Humar et al. (2002) also identified the risk factors of SGF were donor age > 50 years (RR= 3.3), and kidney preservation time > 24 hours (RR=1.6). Moore et al (2007) reported that donor age, donor body mass index, donor hypertension, cause of death, black recipient race, recipient weight and cold ischemia time influenced early graft function.

IGF is clinically defined as creatinine < 3 mg/dl by post-operative day no. 5 (Humar et al. 2002). DGF is a form of acute renal failure resulting in post-transplantation oliguria, increasing in allograft immunogenicity and risk of acute rejection episodes, and decreasing in long-term survival (23). The definition of DGF in clinical studies retrospectively focuses on the basis of renal function and the need of dialysis treatment (Humar et al. 2002). Bronzatto et al. (2009) stated that DGF is found approximately 60% of recipients of kidneys from deceased donors. The possible risk factors of DGF were donor age > 50 years (Boon et al. 2000, Humar et al. 2002, Iglesias-Márquez et al. 2002), kidney preservation time > 24 hours (Iglesias-Márquez et al. 2002, Humar et al. 2002), high panel-reactive antibodies (PRA), donor creatinine >1.7 mg/dl (Humar et al. 2002), CIT > 24 hours (Iglesias-Márquez et al. 2002, Bronzatto et al. 2009) or CIT > 28 hours (Boon et al. 2000), mean arterial blood pressure of less than 100 mm Hg, female donor to male recipient combination, peak panel reactive antibodies of more than 50% (Boon et al. 2000). Additional causes of DGF are antibody-mediated rejection, mechanical complication (eg, urinary leak, obstructing hematoma, and thrombosis of the renal artery or vein), cortical necrosis/infarction, acute calcineurin inhibitor toxicity, thrombotic microangiopathy,

drug-induced interstitial nephritis, and fulminant disease recurrence (Yarlagadda et al.2008).

The factors affected post-transplant renal failures are graft urinary tract obstruction, graft vascular thrombosis, graft renal parenchymal disorders (for example, acute tubular necrosis, acute or accelerated rejection, hyperacute rejection, and scarcely thrombotic-microangiopathy or atheroembolic disease. Based on clinical evidences, DGF manifests the ischemia acute tubular necrosis (ATN). Then, DGF can be classified as ATN if the prerenal, postrenal, renovascular and other parenchymal causes of allograft dysfunction are excluded. The consequences of DGF include reduced patient survival patient, reduced graft survival, increased of acute and chronic rejection, elevated baseline creatinine, procedural complication and financial cost (Walele et al. 2002). Giral-Classe (1998) reported that the long period of delayed graft function, especially more than 6 days, reduced long term graft survivals calculating as a Cockcroft calculated creatinine clearance (cC_{cr}) $\geq$ 10 ml/min.

2.3 Factors influencing the risk for DGF

Walele et al. (2002) and Yarlagadda et al. (2008) summarized the risk factors affected DGF. These variables are from donor, recipient, preservation technique and immune as indicated in Table 2-1.

Table 2- 1 Risk factors for delayed graft function (DGF)

	Immunological factor	Non-immunological factor
Donor		Living or cadaver (brain death) donor Age > 50 years old Expanded criteria donors (ECD) Donation after cardiac death (DCD) Cause of death : Cerebrovascular >trauma Hypotension Inotropic support History of hypertension African- American ethnicity Creatinine clearance (<100ml/min) Biopsy : vascular atherosclerosis
Recipient	Positive crossmatch Panel reactive antibody titer : (PRA) > 50% Human leukocyte antibody (HLA) match /mismatch : HLA > 1 mismatch	Extracellular fluid volume status Perioperative hemodynamics Age > 55 years old Female to male gender African- American ethnicity Primary disease (diabetes) Dialysis modality Hemodialysis > Peritoneal dialysis Previous transplantation History of blood transfusion Duration on dialysis before transplant Increased of thrombosis risk (eg., factor V leiden mutation)
Preservation variables		Static cold storage or machine perfusion Cold ischema time (> 12 hours) Warm ischemia time

Reference : Walele et al. (2002), Yarlagadda et al. (2008)

2.3.1 Non-immunological factors related to the donor

Because this study focused only on cadaveric donor, several criteria of selected cadaveric donor for transplantation need to be considered in details.

2.3.1.1 Cadaveric donor type

Although the living donor may deliver better graft outcomes than the deceased donor, the shortage of kidney is therefore a reason for cadaveric donor selection. Cadaveric donor or brain death cadaver can be classified into two types which are expanded criteria donors or marginal donors (ECDs) and non-expanded donors or standard criteria donor (SCD). The United Network for Organ Sharing (UNOS), USA has defined ECDs as "those donors have been demonstrated to increase the risk of late allograft loss because of certain clinical characteristics". These donor characteristics have the age greater than 50 years, long-standing history of HTN, cerebral vascular accident, the cause of death, terminal serum creatinine greater than 1.5 mg/dL, diabetes, or long CIT (24).

The cadaveric kidneys are theoretically subjected to the cumulative damages at every step along the way from procurement to reperfusion whereas kidneys from living donors rarely develop DGF (25). ECD can help to increase a number of deceased donor kidneys availabilities, shorter waiting times, reduction of morbidity and mortality associated with long term dialysis therapy (Pascual, Zamora and Pirsch, 2008).

Although the use of ECD for kidney transplants has increased worldwide, a number of researches report the problems associated with ECD. Pretagostini et al (2009) indicated that the increased use of ECD shows potentially a risk of DGF. The study was compared the incidence of DGF between SCD (n = 75) and ECD (n = 46). ECD group was composed of older donors ($P < .0001$), with an increased incidence of diabetes mellitus (DM; $P<.0001$), arterial hypertension (AH; $P<.0001$), cerebrovascular accidents ($P = .013$), and lower creatinine clearances (CrCl; $P = .008$). 40 patients (33%) were showed the sign of DGF whom mainly in ECD ($P = .004$). The results showed that donor age >or= 60 years ($P = .005$), CrCl < 40 mL/min ($P = .025$), donor history of DM ($P = .026$) and AH ($P = .017$), and cold ischemia time > 15 hours ($P < .0001$) were factors related to increased incidences of DGF

(Pretagostini et al. 2009). Lai et al. (2009) found that the effect of ECD caused shorter graft longevity. The factors affected DGF were increased donor age, greater cold ischemia time, and presence of an acute rejection episodes. The study covered 46 ECD cases divided as absence of DGF (n = 23) and DGF (n = 23). DGF was composed of older donors (P = .033) with longer cold ischemia times (P = .017), and greater incidences of acute rejection episodes (ARE) (P < .0001). Comparing absence of DGF group with DGF group, the results of 1-year and 3-year overall recipient survivals were 95.7% and 95.7% versus 91.3% and 91.3%, respectively (P = not significant). Additional results showed censored 1-year and 3-year overall graft survivals were 100% and 92.9% versus 85.6% and 79.9%, respectively (P = .026). Collins et al. (2009) reviewed the data from 1991 to 2005 in Australia and New Zealand, followed until December 2006 of the deceased donor kidneys transplant. A number of 3248 recipients of non-ECD kidneys and 781 recipients of ECD kidneys were summarized. The study showed that ECD kidney transplants have more signs of acute rejection and DGF than non-ECD kidneys. However, Hassanain et al. (2009) reported a higher rate of DGF in ECD versus SCD kidneys. The similar detrimental impact on 5-year actual graft survival was founded in SCD and ECD kidneys.

2.3.1.2 Donor age

Due to the insufficient number of kidney availabilities, the donor at any ages is accepted. Previously, older donors who had over 50 years old were not considered suitable. However, the kidneys from such donors are now commonly used if these individuals are in good physical and mental condition and have adequate kidney function. The interesting in DGF has increased with the increased use of marginal donors, including donors at the extremes of age (Oppenheimer et al. 2004, Karachristos et al. 2010). This group of donors experiences DGF more frequently with an incidence of up to 50% (26).

Pretagostini et al. (2009) found that donor age > or = 60 years and cold ischemia time > 15 hours have increased DGF. Collins et al. (2009) stated that for recipients of ECD kidneys, donor age 60 years or above and donor age 50 to 59 years considered as a high and intermediate risk of acute rejection and delayed graft function, respectively. Chavalitdhamrong et al. (2008) compared the allograft and

patient survival between recipients of transplants from older ECDs (age > or = 70) and younger ECDs (age 50-69). The results indicated that recipients from older ECDs have higher overall graft loss (hazards ratio (HR) of 1.37), death-censored graft loss (HR of 1.32) and patient death (HR of 1.37). The risk of patient death was relatively lower when older ECD kidneys were transplanted into recipients older than 60 compared with recipients aged 41 to 60. However, the risk of death-censored graft loss was not increased in older ECD transplants recipients at the age > 60. Increasing donor age has a pronounced negative effect on graft survival. The 5 – year cadaveric graft survival rate ranges from 68% at the donor age of 19 to 30 years old to 44% at the donor age of higher than 60 years old. The percentage of kidneys from donor older than 60 years of age grows from 5% in 1991 to 8% in 1996 (Walele et al. 2002). The increased use of older donors reflected in a 2007 survey of kidney transplant centers in the United States in which almost 60 percent of centers have no policy of age limitation for kidney donors (27). Among the remaining centers, an age of 75, 70, 65, 60, and 55 years have been reported in 4, 5, 21, 7, and 1 percent, respectively. With respect to a lower age limit, most centers report that an age less than 18 years is an absolute exclusion criterion. (27). An increased incidence of delayed graft function among recipients of older donor kidneys and an overall decrease in nephron dosing for an average older donor may explain the poor long-term survival rate associated with this donor group (7). Moreso et al. (1999) demonstrated that donor age > 50 years caused the incidence of DGF (29.1%) calculated from 595 transplant patients and showed the highest risk of late graft loss.

2.3.1.3 Donor health condition

Increased age of donor often associate with decreased in healthy status. This may not be true if the donors are in a good physical and mental condition. In human adults, renal blood flow (RBF) generally declines by approximately 10% per decade after the age of 40. This reduction of RBF is partially explained by a reduction of renal mass but it is accompanied by an increased afferent and efferent arteriolar resistance especially in the renal cortex (28, 29). Kidneys from older individuals have several structural and functional changes compared with kidneys from younger

donors. Other than the donor age, health conditions such as atherosclerotic vascular disease, hypertension, and increased serum creatinine (<100 ml/min) also caused an additional injury of donor kidney (Walele et al. 2002). Studies of kidneys obtained by autopsies have demonstrated a progressive decrease in number and size of glomeruli with age, resulting in a progressive decrease of the glomerular filtration volume (30, 31). Not only factors intrinsically related to the donor, but also events preceding brain death and harvest of the kidney contribute to the occurrence of DGF. Verran et al. (2001) reported the health status of 114 olders over 55 year of age associated with rate of DGF and allograft failure between 1990 and 1997 in New South Wales, Australia. The incidence showed the rate of DGF was 33% associated with cardiovascular disease of donor. After 5-year follow up period, the rate of death censored allograft failure was 24%. This failure was associated with hypertension of donor.

2.3.1.4 Cold ischemia time

Cold ischemia time (CIT) is one of risk factors associated with delayed graft function (DGF) and transplant outcome. CIT is defined as the time from removal of the kidney from cold storage or perfusion with preservation solution in the donor to completion of the renal arterial anastomosis (32). The most important independent and robust risk factor is the time that it takes from the explantation of the kidney until its transplantation into the recipient, defined by the cold ischemia time (CIT) (33-39).

A long CIT, in particular, shows a considerable influence on post-operative graft function. The rate of DGF in grafts with a CIT > 24 hours is 20% higher than the grafts with a shorter ischemic time. (40) Several strategies to reduce CIT have been proposed. Vacher-Coponat et al (2007) reported that the reduction of CIT from 21.45 to 13.27 hours is determined by a timesheet in a French transplant center. The DGF rate is also reduced from 34.7 to 20.7%. The collaboration of all transplantation personnel is needed for implementing an effective timesheet. Hetzel et al. (2002) indicated that reduced CIT minimize the risk of DGF. Harnández et al (2008) reported the data using multivariate Cox analysis and found that CIT was related to death-censored graft loss with a 20% increase for every 5 hours of CIT

(relative risk 1.04, 95% CI :1.01-1.1). Additionally, the risk of graft loss increased higher in CIT > 19 hour group than CIT < 19 hour (RR 1.5; 95% CI : 1.1-2.1)

2.3.2 Non immunological factors related to the recipient

2.3.2.1 Recipient age

Recipient age is a risk factor for DGF especially when kidneys from pediatric donors to adult recipients are involved (41). In general, the oldest and youngest recipients have the worst long term allograft survival rate. The 5-year cadaveric graft survival rate ranges from 57% in patients older than 60 years of age to 65% in patients 31 to 45 years of age. The poor allograft survival rates for older recipients are due in part to the relatively high rate of graft loss because of patient death in this population. Friedman et al. (2004) investigated the patient age of renal transplants ranged from 2 to 68 years. The results showed that the overall rejection within 90 days of cadaveric patients age > 60 and those of < 60 are 6.7% and 37.6%, respectively.

The mean age of recipients of cadaver donor kidneys increases from 42 to 46 years between 1991 and 1997 alone. During this same time period, the percentage of cadaver kidneys transplanted in recipients older than 60 years of age increases from about 5% to 15%. Though older patients have an intrinsically greater post-transplant mortality rate, the impact of age on graft survival may be counterbalanced by the fact that older patients tend to be less immunologically aggressive (7).

2.3.2.2 Recipient health status

Past illnesses or diseases of recipient during pretransplantation lead to end-stage renal disease such as diabetes and hypertension. These multiple organ system manifestations are associated with poorer long-term allograft survival rate than diseases not associated with systemic manifestations, such as polycystic kidney disease and IgA nephropathy. Diabetes is also a common disease developed as increased age. Several publications of diabetic patients related to transplant have studied (Fernández-Fresnedo et al. 2002, Rahul et al. 2004, Gore et al. 2006). Fernández-Fresnedo et al. (2002) evaluated the type I and type II diabetic patients had

the 1- and 3- year survivals of 58%, 50% and 50%, 38%, respectively. The results confirmed that the diabetes patients either Type I or Type II have lower survival graft than the non-diabetes patients. Rahul et al. (2004) reported that obesity influences the risk for DGF and local wound complication. Comorbid factors associated with obesity results in premature death with a functioning kidney transplant. Gore et al. (2006) demonstrated that of 27377 patients, the factors affected obesity associated with older age, female gender, African American race and increased comorbidity.

2.3.2.3 Immunological factors associated with recipients

The immunology blood test is an important tool for preoperative kidney transplantation. Several blood tests must be performed such as HLA –matching and panel reactive antibodies.

The human leukocyte antigen (HLA) system is synonymous with the human major histocompatibility complex (MHC). These terms are described by a group of genes on chromosome 6 that encode a variety of cell surface markers, antigen-presenting molecules, and other proteins involve in immune function. HLA-matching effect continues to play a role on the long-term loss rate. The 5-year graft survival rate decreases in a step-wise fashion from 69% for patient with O-A, B, and DR mismatches to 57% for completely mismatched grafts (five or six HLA-mismatched antigens) (42). Lee et al. (2008) found that recipients of zero HLA mismatch kidneys with less than 36 hours of cold ischemic time had 75% of 5- year graft survival compared to 67% of recipients with one or more mismatches kidney.

Panel reactive antibodies (PRA) are another key marker for transplantation. The lower occurrence rate of DGF with zero HLA mismatch and low levels of panel reactive antibodies (42), suggested that immune factors are responsible for this relation. In addition, the use of calcineurin inhibitors is a risk factor because their vasoconstrictive properties influence renal perfusion and enhance ischemic damage (43).

2.3.3 Factors related to the transplantation procedure

2.3.3.1 Organ status

The procurement of kidney organ during preoperative transplants needs an essential procedure to maintain the kidney function. Organ procurement also contributes to the development of DGF.

2.3.3.2 Warm ischemic time

Warm ischemia time (WIT) refers to the period between circulatory arrests and commencement of cold storage. Interestingly, WIT is increased in donation after cardiac death. Based on the modern in situ perfusion techniques, the warm ischemia time is essentially zero, although there is warm ischemia if hemodynamic deterioration or cardiac arrest occurs before harvest (32). This starts with hypoperfusion after circulation of the donor has stopped. WIT nowadays becomes a serious contributor to DGF (44, 45) and posttranplant acute tubular necrosis (ATN) (Yarlagadda et al. 2008).

2.3.3.3 Surgical error

Even the procedure of kidney transplantation is a routine operation several mistakes could affect the outcomes of graft and patient. Therefore, the prevention of any types of errors could be monitored and well prepared for efficient and successful transplantation. Breza and Navratil (1999) reviewed the surgical factors affected the graft survival. The graft may be lost during surgery. Additionally, the consequences of surgical error may be uraemia, dialysis treatment with anticoagulation, immunosuppression, acute thrombosis of renal artery and vein, stenosis of renal artery, rupture of transplanted kidney, lymphocele and bleeding into the vicinity of the renal graft. Meier-Kriesche et al. (2000) analyzed 73,103 adult renal transplants from 1988 to 1997 and found that longer waiting time on dialysis is a risk factor for death censored graft survival and patient death with functioning graft after renal transplantation. The waiting time of 6 to 12 months, 12 to 24 months, 24 to 36 months, 36 to 48 months and over 48 months increased the mortality risk of 21, 28, 41, 53 and 72%, respectively.

2.3.4 Immunosuppressive therapy

The application of immunosuppressants is needed for kidney transplantation. However, the optimal maintenance immunosuppressive therapy in renal transplantation has not been established (46). Browne et al. (2003) reported that adult cadaveric renal transplants were treated with sequential drug immunotherapy having better recovery of renal function. The major immunosuppressive agents that currently being used are corticosteroid, azathioprine or mycophenolate mofetil (MMF), cyclosporine, tacrolimus, and rapamycin have been used increasingly. Based on the data of renal transplantation in Siriraj Medical School Hospital from 1973 to August 2001, 103 patients were from living related donors and 278 patients were from cadaveric donors. The rate of graft survival for 1,2.5 and 10 years were significantly found in CyA group than azathioprine group (2).

2.3.4.1 Corticosteroids

Corticosteroids have played a central role in transplantation since the 1960s. The side effect profiles of corticosteroids are well documented. However,the side effects of corticosteroids include acne, Cushingoid facial appearance, hirsutism, mood disorders, glucose intolerance, hypertension, cataracts, and osteoporosis. Oral maintenance doses of 5 to 10 mg per day are commonly administered for the life of the allograft. Alternate day dosing may reduce corticosteroid side effects. Efforts to withdrawing corticosteroids completely have been plagued by increasing risks of acute rejection and graft loss in long-term (47).

2.3.4.2 Mycophenolate mofetil (MMF)

Mycophenolate mofetil impairs lymphocyte function by blocking purine biosynthesis via inhibition of the enzyme inosine monophosphate dehydrogenase. MMF has been developed to replace for azathioprine. MMF is used to rescue therapy in patients with rejection episodes refractory to OKT3. It is not nephrotoxic agent and has less bone marrow toxicity than azathioprine. However, gastrointestinal toxicity is usually manifested by gastritis and diarrhea. Maintenance doses of MMF are 750 to 1,500 mg twice daily. Monitoring of MMF blood levels is not clinically available and indicated for most patients. Clinical trials demonstrated

that, when using in combination of cyclosporine or tacrolimus, MMF is 50% more effective than azathioprine in preventing episodes of acute rejection (48).

2.3.4.3 Cyclosporin

Cyclosporin has been introduced in the early 1980s. The use of cyclosporin improves outcomes in transplantation. The regimen is changed after trials that show improvement of allograft survival with cyclosporine therapy (49, 50). The long-term efficacy of cyclosporin is accepted in trial compared to the effects of different immunosuppressive agents (51). However, no research has been reported the optimal maintenance dose of cyclosporin. Another important consideration is that several drugs interfere with its metabolism, and therefore may cause either overdosing with deterioration of renal function or underdosing with the increasing in an incidence of rejection. Moreover, there is a meta-analysis finding that cyclosporine withdrawal is associated with the increasing in an incidence of acute rejection, but not in reduction of long-term graft survival (47).

2.3.4.4 Tacrolimus (FK506)

Tacrolimus is a macrolide that possesses similar but slightly more potent than cyclosporine. The recent cases have shown similar graft survival outcomes with tacrolimus, when compared to cyclosporin-based regimens in the setting of renal transplantation (52). The incidence of acute rejection and requirement for intensive immunosuppression may be less with tacrolimus (53). Tacrolimus has a toxicity profile slightly different from that of cyclosporine. Both short-and long-term studies in renal transplant recipients suggested that tacrolimus is at least as nephrotoxic as cyclosporine. Moreover, it is found a markedly increase of insulin dependent diabetes mellitus. Differences in toxicity with tacrolimus as compared to cyclosporine include more prominent neurologic side effects, more frequent incidence of post-transplant diabetes, less frequent hirsutism, gingival hyperplasia, and hypertension (54).

2.3.4.5 Calcineurin inhibitors

Calcineurin, a calcium and calmodulin-dependent serine-threonine phosphatase, has recently been demonstrated to participate in signal transduction. The calcineurin inhibitors inhibit directly on phosphates activity. Calcineurin inhibitors are composed of cyclosporine and tacrolimus, which currently serve as the backbone of solid organ transplant immunosuppression (55). The calcineurin inhibitors differ from their predecessor immunosuppressive drugs by their selective inhibition of the immune response. Inhibition of calcineurin impairs the expression of several critical cytokine genes that promote T cell activation. These genes include IL-2, IL-4, IFN-gamma, and TNF-alpha(55).

2.3.4.6 Anti-lymphocyte antibody

The monoclonal (anti-lymphocyte; OKT3) and polyclonal antibodies (anti-thymocyte globulin; ATG) have been used as induction therapy in high risk patients. Abou-Jaoude and Almawi (2003) administered 26 patients with anti-thymocyte globulin-fresenius (ATG-F) as a single intra-operative bolus induction therapy and 17 patients with extended ATG-F. The results indicated that ATG-F is an effective induction agent for kidney transplantation. Bunnapradist and Takemoto (2005) evaluated the induction of antibody therapy to 24901 transplants reported to the United Network for Organ Sharing (UNOS) during 1999 to 2001. The antibodies used are Thymoglobulin (polyclonal rabbit aginst human thymocytes, Sangstat, Fremont, Calif, USA), Simulect (basiliximab, Novartis, Basel, Switzerland) and Zenapex (antagonist of interleukin-2 receptor or daclizumab, Hoffman-La Roche,Basel, Switzerland). The results showed that the patients receiving Thymoglobulin were more sensitized, retranplanted or DGF with the propensity scores of 1.50%, 1.51% and 1.75%. Thymoglobulin also reduced the odds of rejection compared to Simulect and Zenapex.

2.4 Outcomes of Renal Transplantation

2.4.1 The Anti-Allograft (Rejection) Response

Renal-allograft rejection depends on the coordinated activation of alloreactive T-cells and antigen-presenting cells (e.g., monocyte-macrophages,

dendritic cells, and B cells). In contrast, acute rejection is a T-cell dependent process, a broad array of effect mechanisms participate in the destruction of the allograft. The anti-allograft response occur from a diverse assembly of lymphocytes including CD4+ T-cells, CD8+ cytotoxic T-cells, antibody-forming B-cells, and other proinflammatory leukocytes with the release of cytokines and cell-to-cell interactions.

2.4.1.1 Antigenic Stimulation

T-cell activation is an incompletely understood process begins when T-cells recognize intracellular processed fragments of foreign embedded in the groove of the major histocompatibility complex (MHC) proteins expressed on the surface of antigen-presenting cells (20, 18). The T-cell antigen recognition complex is formed by the clonally variant immunoglobulin-like T-cell receptor and peptide chains that recognize the antigenic peptide in the context of MHC proteins, and clonally invariant CD3+ chains that initiate intracellular signals originating from antigenic recognition. It is likely that some of the recipient's T-cells recognize the allograft directly, that is, they recognize donor antigenic peptides presented on the surface of donor antigen presenting cells. Whereas other T-cells recognize the donor antigen only after it is processed and presented by the recipient's antigen-presenting cells (56).

CD4+ and CD8+ proteins are expressed on reciprocal peripheral-blood T-cell subgroups which bind to the monomorphic component of HLA class II and class I molecules, respectively. Antigenic recognition stimulates a redistribution of cell surface proteins and a clustering of the complex of T-cell antigen receptor and CD3+ with CD4+ or CD8+ antigen (57).

On stimulation with antigens, the complex of T-cell antigen receptor and CD3+ and CD4+ and CD8+ proteins activate several intracellular-protein tyrosine kinases (18, 63). Tyrosine phosphorylation of phospholipase C activates coenzyme and initiates the hydrolysis of phosphatidylinositol 4, 5-biphosphate but accelerates the generation of inositol 1,4,5-triphosphate and diacylglycerol. Inositol triphosphate, in turn, mobilizes ionized calcium from bound intracellular stores, whereas diacylglycerol, in the presence of increasing cytosolic free calcium, activates protein kinase C (58).

2.4.1.2 Costimulatory Signals

T-cell requires two separate signaling channels before activation occurs. The first signal is antigen specific and is provided by the interaction of T-cell receptor with peptide antigen presented within the antigen binding groove of MHC molecules. The second signal is provided by the interaction of T-cell surface molecules with their ligands on antigen presenting cells. T-cell activation, as measured by interleukin-2 production and proliferation in vitro, requires both antigenic and costimulatory signals engendered by cell-to-cell interactions among antigen-specific T cells and antigen-presenting cells. Cytokines are derived from antigen-presenting cells (e.g., interleukin-1 and interleukin-6) can provide costimulatory signals resulting in T-cell activation in vitro. The delivery of both antigenic and costimulatory signals leads to stable transcription of the interleukin-2 gene and other pivotal T-cell activation genes. The foregoing costimulatory signals depend on protein kinase C and calcium and are sensitive to cyclosporine and tacrolimus (59).

The stimulation of B-cells also depends on the antigenic signal and the costimulatory signals. The antigenic signal is generated by the interaction between the specific antigen and the cell-surface immunoglobulin. T-cell derives cytokines (e.g., interleukin-2 and interleukin-4), physical contact between T-cells and B cells through specific pairs of receptors and coreceptors, or both. The interaction provides the signals essential for B-cell stimulation (60).

2.4.1.3 Interleukin-2-Stimulated T-Cell Proliferation

Autocrine T-cell proliferation occurs as a consequence of the expression of interleukin-2 that depends on T-cell activation and the multimeric high-affinity interleukin-2 receptors formation by the noncovalent association of three distinct interleukin-2-binding peptides. Interleukin-2 triggers the activation of protein tyrosine kinase and phosphatidylinositol-3-kinase (a novel lipid kinase) and the translocation into the cytosol of Raf-1 serine-threonine kinase bound to interleukin-2 receptors. These events lead to the expression of several DNA-binding protein including c-jun, c-fos, and c-myc, as well as the progression of cell cycle (61).

The net consequences of cytokine production and the acquisition of activation-induced cell-surface receptors is the emergence of antigen-

specific, graft-infiltrating, and destructive T-cells. Cytokines also facilitate the activation of macrophages and other inflammatory cells and the production of anti donor antibodies by stimulating of B-cells. Moreover, cytokines can amplify the ongoing immune response by up-regulating the expression of human leukocyte antigens (HLA) and costimulatory molecules (e.g., B7) on graft parenchymal cells and antigen-presenting cells (62).

2.4.2 Graft survival

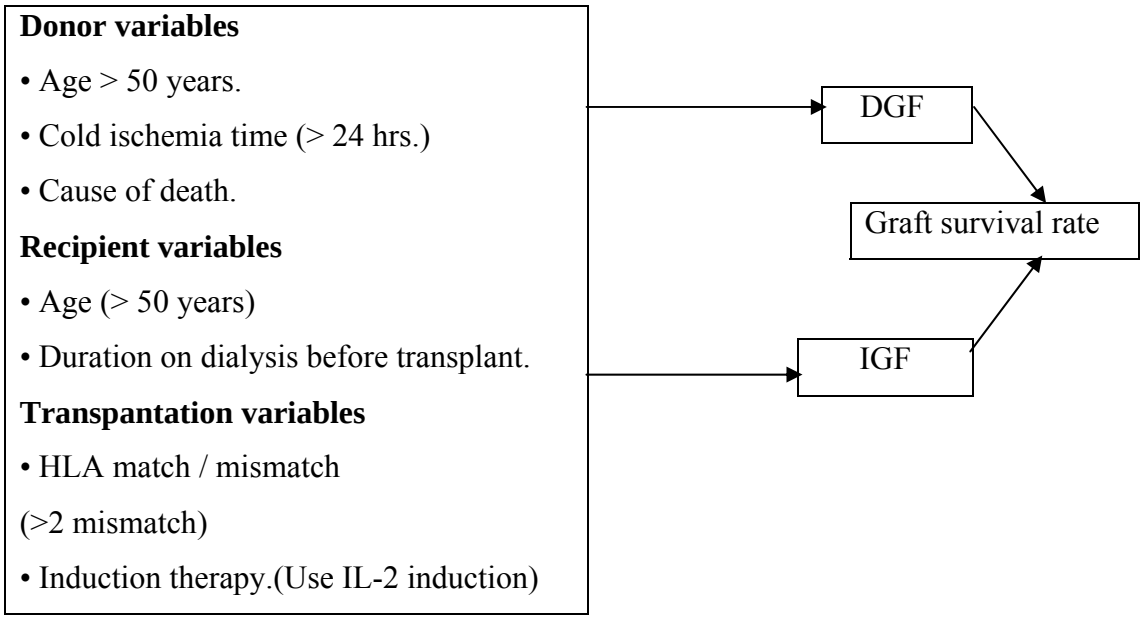
The successful outcome of cadaveric kidney transplant is determined by the rate of graft survival. Tejani et al. (1999) reviewed the 5272 transplants in children between 1987 and 1996. Of these numbers, 2486 were living donors and 2786 were cadaveric donors. The graft survivals for cadaveric patients with DGF and no DGF were 83.8% and 68.7%, respectively. This study confirmed that DGF is a major risk factor for renal graft failure. The risks of graft loss are dependent on time of posttransplantation (Prommool et al. 2000). Hetzel et al. (2002) demonstrated that graft survival after 7 years are associated with donor age, recipient age and postoperative DGF. The results showed that the older donors (over 60 years) and younger donors have the rate of graft of 44% and 65%, respectively. Pieringer and Biesenbach (2005) studied the risk factors or delayed graft function and graft survival. The results showed that the 3 years of graft survival in the DGF group (74.2%) seem to be lower the IGF group (84.4%). If expanded criteria donor (ECDs) and donation after cardiac death (DCD) used for transplants, the results showed that the kidneys obtained from these two sources caused higher incidence of DGF, longer time to reach serum creatinine below 3 mg/dl, longer length of hospital stay and readmission to the hospital, compared to the standard criteria donors. After 50 months of follow-up, the graft survival was lower in the ECD group (Saidi et al. 2007). The length of graft survival can be extended by the use of antibody induction (Bunnapradist and Takemoto, 2005). The differences were found in the study of Bronzatto et al (2009) who reported after 1 year follow-up, the DGF group showed worse graft function and high rate of graft loss. McLaren et al. (1999) indicated that the combination of DGF and acute rejection gave the worst short term graft survival at 1 year of 68%, compared to 92% of the graft with no DGF or acute rejection.

2.4.3 Patient survival

The ultimate goal of patients with end-stage renal disease is extended their survival. A number of researches have identified the risk factors among donor characteristics affected short and long term graft survival (Tian, Liao and Chen, 2008). Hetzel et al. (2002) reported that patients at the age of < 40 years, 40-60 years and > 60 years have the survival rate of 91%, 79% and 58% after 7 years of transplantation. Emiroğlu et al (2005) found that the graft survival at 1-,3- and 5- years without acute rejection within the first 6 months after transplantation of the patients age < 50 years versus those age > 50 years are 95% versus 90%, 65% versus 60%, and 40% versus 35%, respectively. Compared to the graft survival at 1-,3- and 5- years with acute rejection, the results of patients age < 50 years versus those age > 50 years are 93% versus 89%, 71% versus 55%, and 44% versus 28%, respectively. Okamoto et al. (2009) analyzed 601 cases of kidney transplantation during 35 years at Japanese single center. The results showed the donor survival rate at 5, 10, 20, 30 years are 98.3%, 94.7%, 86.4% and 66.2%, respectively. Kyllönen et al (2000) investigated 1047 cadaveric transplants during 1991-1997 and found that the rates of 1- and 5 – year patient survival were 96% and 88% while those of 1-and 5- year graft survival were 92% and 78%. The onsets of DGF are due to donor age, cause of death, type of graft perfusion and cold ischemia time, and type and length of dialysis.

Conceptual Frame Work

Independent variables **Dependent variables**



CHAPTER III
MATERIALS AND METHODS

3.1 Study Population

The study was conducted at Siriraj Medical School Hospital which is a 2,500-bed university hospital in Bangkok and is one of the largest kidney transplantation centers in Thailand. A total of 147 medical records of kidney transplant recipients, who underwent cadaveric kidney transplantation obtained from the transplant registry of the Siriraj Medical School Hospital Organ Transplantation Center were collected and reviewed for 7 years starting from January, 2002 to January, 2009. Eligible patients were followed up at least 6 months postoperatively until end of the study on 31st January 2009.

3.2 Sample selection

The criteria of selected patients are based on two categories. The one is inclusion criteria and the other is exclusion criteria.

The inclusion criteria focus on the age of patient. The medical records of all consecutive patients aged at least 18 years old who initially had undertaken kidney transplantation were collected.

The exclusion criteria cover three groups of recipients. The first group is recipients of multi-organ transplants or dual kidney transplants. The second group is recipients who had graft failure or death within 3 months which might be caused by complications of the kidney transplant operation. The last group is recipients who had follow-up time less than 6 months or died before 6 months.

3.3 Sample size estimation

The study was conducted by using a retrospective cohort design. A number of sample size (or renal transplant recipient) used in this experiment were 77 recipients calculated based on the following formula:

$$n = \frac{Z^2_{\alpha/2} p\,(1-p)}{d2}$$

Where n is an estimated sample size

α is the probability of type I error using α = 0.05 (=1.96 from Table XX)

p is the proportion of hazard rate based on the formula of 1- graft survival rate post CD-KT at 5 years where the graft survival rate is 0.53

q is 1-p

d is the margin of error in estimating proportion of graft survival rate = 25 % calculated as 25%*q = 0.1175

Thus;

$$n = \frac{(1.96)^2 0.53)\,(0.47)}{(0.1175)^2} = 69.34$$

In this study, a percentage of drop out of 10% were used. Therefore, n is 77.

3.4 Methods

3.4.1 Screening of the potential renal transplant recipient

Due to a shortage of donated organs and a large numbers of patients on waiting list for transplantation, therefore, it is very important to select carefully an appropriate renal transplant recipient. The decision was made by the transplantation team. No contraindications of renal transplantation were used in this study. These included uncontrolled cancer, HIV positivity, active systemic infection and/or any condition with life expectancy less than 1 year, poorly controlled psychosis, and active substance abuse (13). Three risk factors associated with the recipients considering as independent variables were accessed. They were the age of the recipients who must be $\geq$ 18 but < 50 or $\geq$ 50 years old and gender (male or female) and the duration of dialysis before transplantation. The duration time was calculated by subtracting first dialysis date by renal transplant operation date (months) and identified as < 24 or $\geq$ 24 months.

3.4.2 Screening of potential cadaveric donor

Due to the low availability of living kidney donor, the cadaveric donors were chosen for this study. Both the short-term surgical risk and the long-term risks of having a single kidney must be carefully defined. Specific examinations of male and female patients were performed. The male patient needed to follow a testicular examination, a measurement of prostate specific antigen for those who aged of 50 years old, and having a digital rectal examination. The female patient must be tested for breast examination, mammography, pelvic examination, and papanicolaou smear. Although there is a substantial criteria used to exclude potential donors, generally accepted absolute contraindications including the presence of one or more of the following clinical characteristics: proteinuria and/or hematouria, impaired renal function, HIV infection, active malignancy, chronic illness, particularly chronic pulmonary disease or cardiac disease, poorly controlled psychosis, active substance abuse, and pregnancy (15).

For cadaveric kidney transplantation, most donors are brain-dead cadavers whereas the heart is still beating. Because of the limited numbers of available kidneys, the potential cadaveric donors should be free from any contraindications including chronic renal diseases, age more than 70 year, potentially metastasizing cancer, severe hypertension, bacterial sepsis, HIV infection, and oliguric acute renal failure. In this study, the independent variables for cadaveric donor were determined. The variables were the donor age (< 50 or ≥ 50 years old), cause of death, and cold ischemia time. The cold ischemic time referred to the storage time (hours) of harvested kidney at cold temperature. This time was categorized into ≤ 24 or >24 hours.

3.4.3 Performing of blood immunology test

The immunological data was performed to ensure that both donor and recipient are suitable for kidney transplantation. The human lymphocyte antigen (HLA) typing of both donors and recipients were identified at the Organ Donation Center of Thai Red Cross Society, Bangkok.

3.4.4 Determination of factors associated with transplantation .

The outcomes of transplantation observed in this study were classified as graft non function (GNF), immediated graft function (IGF) and delayed graft function (DGF). The GNF cases were excluded from this study. The diagnostic included an increasing, remaining/unchanging, or decreasing of the serum creatinine level by less than 3 mg/dl after 5 days of post-transplant.

IGF was defined as the patients had no sign of DGF or SGF which determined by the serum creatinine < 3 mg/dl by post-operative day 5 (Humer et al. 2002, Moore et al. 2007). DGF was defined as the requirement of dialysis in the first week after surgery (Humer et al. 2002, Moore et al. 2007). In this study, IGF also classified as non-DGF.

The induction therapy was identified whether the recipients had received any types of these treatments, for example, Basiliximab, Rituximab and Daclizumab.

3.4.5 Evaluation of Time-fixed covariate

Numbers of time-fixed for recipient, donor, and transplant-related characteristics were evaluated at baseline. The date of pre- and postoperation were evaluated as risk factors of DGF. The following recipient covariates were assessed: age, gender and duration of dialysis before transplantation. Donor's covariates included age, gender and cause of death. Transplant covariate's included duration of cold ischemic time, and number of human leukocyte antigen (HLA) mismatches at A-, B-, and DR-loci, percentage of PRA and induction therapy of IL-2.

3.4.6 Determination of the outcome of transplantation

Three outcomes of transplantation were identified. These were the prevalence rate of delayed graft function after transplantation, the graft survival rate in DGF patients after transplantation, and the graft survival rate in patients who had DGF and non DGF among renal allograft recipients.

Graft survival is censored for patient death with functioning graft. Renal function at one year is calculated using the Cockroft- Gault formula (23). Allograft failure is usually defined either by the patient's death or the patient's need to undertake new treatment for end-stage renal disease (ESRD) (for example, chronic dialysis or retransplantation) (24).

3.5 Statistical Analysis

Descriptive statistics were used to explain the demographic data of the sample indicating in 3.2.1 and presented the results in the form of frequency and percentage. The risk was expressed as odd ratio (OR), 95% confidence interval and p-value.

The Kaplan–Meier survival analysis used to evaluate graft survival rate in DGF patients and non-DGF patients after transplantation and the log-rank test was employed to compare the survival rate between groups. All data were analyzed by the SPSS software package (15).

3.6 Ethical Approval

The proposal was be reviewed and approved by the Institutional Ethics Committee, Faculty of Medicine, Siriraj Medical School Hospital, Mahidol University. The information from the relevant transplant medicals records was collected during the studied period as indicated above.

CHAPTER IV
RESULTS

4.1 Demographic data of cadaveric kidney transplantion.

This study focused only on cadaveric kidney transplantation at Siriraj Medical School Hospital, Bangkok, Thailand between January 2002-January 2009. A total of 147 patients with cadaveric kidney transplantation were determined. Patients displaying graft non function (GNF), immediate graft function (IGF), and delayed graft function (DGF) were evaluated the following variables: Recipient: age, gender, duration of dialysis, Donor: age, gender, cause of death, and Transplantation related factors: cold ischemia time, HLA mismatch, panel reactive anti-HLA antibody (PRA), indicating in Table 4-1.

Results showed that 7 patients with graft non function (GNF) were excluded from this study. Of the remaining 140 patients with finally functioning renal graft, 27 patients showed immediate graft function (IGF) (male = 13 (17.3%) and female =14 (21.5%)) and 113 patients indicated delayed graft function (DGF) (male = 62 (82.7%) and female = 51(78.5%)). The incident rate of DGF was 80.7%.

Based on the recipient group, age was divided into < 50 years and $\geq$50 years. Results showed that 106 recipients had age < 50 years (IGF =20 (18.9. %) and DGF = 86(81.1%)) and 33 recipients had age $\geq$ 50 years (IGF= 6 (18.2%) and DGF = 27(81.8%)), respectively. A number of females were found higher in IGF group (21.5% n= 14), but lower in DGF group (78.5%, n=51). The time of hemodialysis of patients who were on dialysis until to time at transplant were 18 (6 (33.3%) in IGF versus 12 (66.7%) in DGF) had $\leq$ 24 months and 84 (9 (10.7%) in IGF versus 75 (89.3%) in DGF) had > 24 months of dialysis.

On the cadaveric donor side, the kidneys were received from male, female and unidentified gender of 91, 36 and 20. Two groups of donor aged < 50 and $\geq$ 50 years were 85 (18(21.2%) in IGF versus 67 (78.8%) in DGF) and 19 (3 (15.8%) in IGF versus 16(84.2%) in DGF). The causes of death of cadaveric donor were 63 from traffic

accident (12 (19%) in IGF versus 51 (81%) in DGF), 17 from CVA (2 (11.8%) in IGF versus 15(88.2%) in DGF), 30 from head injury (7 (23.3%) in IGF versus 23 (76.7%) in DGF), and 30 from others (6 (20%) in IGF versus 24 (80%) in DGF).

Factors related to transplantation included cold ischemia time (CIT), HLA match/mismatch, PRA, and induction of IL-2. Results indicated that 96 had CIT $\leq$24 hours (20 (20.8%) in IGF versus 76 (79.2%) in DGF) and 34 had CIT > 24 hours (5 (14.7%) in IGF versus 29 (85.3%) in DGF). The matching of human leukocyte antibodies (HLA) was separated into < 3 and $\geq$ 3 mismatches. 64 of < 3 mismatches (14 (21.9%) in IGF versus 50 (78.1%) in DGF) and 63 of $\geq$ 3 mismatches were identified (12 (19%) in IGF versus 51 (81%) in DGF). The status of PRA scores were 124 had PRA < 30% (23(18.5%) in IGF versus 101(81.5%) in DGF) and 16 had PRA $\geq$ 30% (4 (25%) in IGF versus 12 (75%) in DGF). A number of patients who received IL-2 inhibitor prior to operation were 45 (7 (14.6%) in IGF versus 38 (84.4%) in DGF), while 95 patients did not have IL-2 medication (20 (21.1%) in IGF versus 75 (78.9%) in DGF).

Table 4-1 Demographic characteristics influencing the outcomes of transplantation

Valiable	IGF		DGF	
	N(27)	%	N(113)	%
Recipient				
Age *years.*				
< 50	20	18.9	86	81.1
≥ 50	6	18.2	27	81.8
Gender				
Male	13	17.3	62	82.7
Female	14	21.5	51	78.5
Duration of dialysis (*month*)*				
≤ 24	6	33.3	12	66.7
> 24	9	10.7	75	89.3
Donor*				
Age *years*.				
< 50	18	21.2	67	78.8
≥ 50	3	15.8	16	84.2
Gender				
Male	19	21.1	71	78.9
Female	6	18.2	27	81.8
Cause of death				
Traffic	12	19	51	81
CVA	2	11.8	15	88.2
Head injury	7	23.3	23	76.7
Other	6	20	24	80
Transplantation related.				
Cold ischemia time. *Hours**				
≤ 24 hours.	20	20.8	76	79.2
> 24 hours.	5	14.7	29	85.3
HLA mismatch				
0,1,2	14	21.9	50	78.1
≥3	12	19	51	81
PRA				
< 30	23	18.5	101	81.5
≥ 30	4	25	12	75
Induction IL-2				
Yes	7	14.6	38	84.4
No	20	21.1	75	78.9

*Totals vary because of missing data.

4.2 The univariate analysis for the association between risk factors and Deleyed graft function.

Each of factors (recipient, donor and transplantation) associated with graft function were analyzed by the method of univariate analysis. All analysis data were presented as odd ratios (OR), 95% confidence interval and p-values, as shown in Table 4-2, 4-3 and 4-4. In this study, seven cases of recipients where the graft non function existed were excluded from the calculation, therefore, two groups of patients displaying IGF and DGF were determined.

Based on 140 cadaveric recipients, results indicated that recipient age and gender did not cause any significant risks of incidence of DGF (p-value of 0.930 and 0.530). However, the duration of dialysis was associated with DGF, was significant(OR= 4.167,95%CI=1.260-13.83,p-value=0.020) (Table 4-2).

Table 4-2 Association between recipient factors and Deleyed graft function.

Valiable	IGF		DGF				
	N(27)	%	N(113)	%	OR	95%CI	*p-value***
Recipient							
Age *years.* *							
< 50	20	18.9	86	81.1	1		
≥ 50	6	18.2	27	81.8	1.05	.38-2.87	0.930
Gender							
Female	14	21.5	51	78.5	1		
Male	13	17.3	62	82.7	1.31	.56-3.03	0.530
Duration of dialysis (*month*)*							
≤ 24	6	33.3	12	66.7	1		
> 24	9	10.7	75	89.3	4.17	1.26-13.83	*0.020*

*Totals vary because of missing data.

** p-value from chi square test.

The statistical results showed that donor factor in terms of age, gender and causes of death did not have any significant effects on the incidence of IGF or DGF (Table 4.3).

Table 4-3 Association between donor factors and Delayed graft function.

Valiable	IGF		DGF				
	N(27)	%	N(113)	%	OR	95%CI	*p-value*
Donor*							
Age *years* .							
< 50	18	21.2	67	78.8	1		
≥ 50	3	15.8	16	84.2	1.43	.38-5.46	0.598
Gender							
Female	6	18.2	27	81.8	1.21		
Male	19	21.1	71	78.9	1	0.43-3.34	0.721
Cause of death							
Traffic	12	19	51	81	1		
CVA	2	11.8	15	88.2	1.77	.35-8.8	0.488
Head injury	7	23.3	23	76.7	0.77	.27-2.22	0.632
Other	6	20	24	80	0.94	.32-2.81	0.913

*Totals vary because of missing data.

** p-value from chi square test.

The results showed that DGF was associated with older donor (age >50 years), but not significance differences between DGF and IGF (p-value = 0.598). Among all causes of death, CVA found to be dependently associated with DGF, but not significant differences (p-value = 0.488).

Four transplantation factors studied were CIT, HLA mismatch, PRA and the induction of IL- 2 therapy. The statistical analysis revealed that all factors related to transplantation had no significance effects on the cause of DGF (Table 4.4).

Table 4-4 Association between Transplantation factors and Deleyed graft function.

Valiable	IGF		DGF				
	N(27)	%	N(113)	%	OR	95%CI	*p-value***
Transplantation related.							
Cold ischemia time. *Hours**							
< 24 hours.	17	20.5	66	79.5	1		
≥ 24 hours.	8	17	39	83	1.26	0.496-3.179	0.631
HLA mismatch							
0,1,2	14	21.9	50	78.1	1		
≥3	12	19	51	81	1.19	.50-2.82	0.693
PRA							
< 30	23	18.5	101	81.5	1		
≥ 30	4	25	12	75	0.68	0.20-2.31	0.540
Induction IL-2							
Yes	7	14.6	38	84.4	1		
No	20	21.1	75	78.9	0.69	.27-1.78	0.443

*Totals vary because of missing data.

** p-value from chi square test.

Transplantation factors contributed to DGF were CIT ≥ 24 hours, HLA mismatch ≥ 3 mismatch and PRA ≥ 30 %. The induction of IL- 2 therapy resulted in reduction of DGF (OR 0.69, p-value= 0.443). However, no significant differences were found in the transplantation factors of CIT, HLA mismatch, PRA, and IL- 2 induction (p value= 0.631, 0.693, 0.540 and 0.443).

4.3 The multivariate analysis for the association between impact factors and Deleyed graft function.

Based on the multivariate logistic regression, the adjusted results found that the patients on hemodialysis > 24 months was significantly associated with DGF (OR adjusted =10.484, 95% CI =1.92-57.31, and p-value = 0.006). The donor age ≥ 50 years was highly related to the incidence of DGF when compared to the donor age < 50 years (OR adjusted =3.782, CI =0.236-60.663, and p-value = 0.347) (Table 4-3).

The transplantation factors of CIT >24 hours (OR adjusted= 2.219, CI =0.330-14.920 and p-value = 0.412) and no induction of IL-2 (OR adjusted= 3.782, CI .236-60.663 and p-value = 0.347) were associated with DGF (Table 4-5).

Table 4-5 Logistic regression between risk factors and Deleyed graft function.

Valiables	OR adjust	95%CI	*p-value*
Recipient			
Age *years.* *			
< 50	1		
≥ 50	1.22	.28-6.17	0.813
Duration of dialysis (*month*)*			
≤ 24	1		
> 24	10.47	1.93-56.74	*0.006*
Donor*			
Age *years*.			
< 50	1		
≥ 50	3.88	.34-43.96	0.273
Cause of death			
Traffic	1		
CVA	0.72	.04-12.23	0.821
Head injury	0.48	.09-2.67	0.477
Other	0.43	.05-3.52	0.432
Transplantation related.			
Cold ischemia time. *Hours**			
≤ 24 hours.	1		
> 24 hours.	2.22	.33-14.92	0.412
HLA mismatch			
0,1,2	1		
≥3	0.91	.18-4.51	0.904
PRA			
< 30	1		
≥ 30	0.67	.07-6.03	0.714
Induction IL-2			
Yes	1		
No	1.10	.23-5.07	0.933

*Totals vary because of missing data.

4.4 The survival analysis of factors associated with graft function

The success of transplantation is directly measured by the survival of graft. This study had follow-up the graft function up to 7 years. The analysis results by Kaplan-Meier estimating for patients with IGF and DGF. There was significant difference in graft survival rate between patients with IGF and DGF (*P=0.016*). However, the graft survival rate found lower in DGF group than IGF group (Figure 1).

Results also revealed that recipients received young kidney donor aged < 50 years had better graft survival rate compared to the kidney from elderly donor aged ≥ 50 years. However, no significant difference was associated with these two age groups of donor (*P= 0.543*) (Figure 2).

Of 4 different causes of donor death, the donor with CVA showed lower in graft survival rate than others. No significant difference of survival rate was found among traffic, CVA, head injury and others (*P=0.425*).

Other transplantation factors, such as CIT, HLA mismatch, PRA and induction of IL-2 did not show significant difference in relationship to the graft survival rate (*P= 0.105*). Among 4 different transplantation related factors, the group having shorter time of CIT < 24 hours showed better survival rate than the other group having CIT ≥24 hours (Figure 3). The induction of IL-2 (Zenapax, Simulet and others) also showed no significant effect on the survival rate (*P*= 0.451) (Figure 4).

The graft survival rate in DGF during 3, 5 and 7 years had lower than non DGF was 69.2, 64.3 and 56.3%, respectively (Table 4.6).

Table 4-6 Graft survival rate at (%) 3, 5 and 7 years classify by variables.

Valiable	3 years.		5 years.		last time		
	SR	**SE**	**SR**	**SE**	**SR**	**SE**	***p-value***
Donor*							
Age *years* .							*0.543*
< 50	81.80	<4.9>	74.20	6.90	74.20	6.90	
≥ 50	66.10	<16.5>	66.10	<16.5>	66.10	<16.5>	
Cause of death							*0.425*
Traffic	79.10	<5.7>	71.80	7.30	57.40	14.10	
CVA	60.90	<14.7>	60.90	<14.7>	60.90	<14.7>	
Head injury	73.90	<14.9>	73.90	<14.9>	73.90	<14.9>	
Other	62.10	<11>	62.10	<11>	62.10	<11>	
Transplantation related.							
Cold ischemia time. *Hours**							*0.105*
< 24 hours.	75.90	<5.6>	75.90	<5.6>	63.30	12.50	
≥ 24 hours.	66.60	<9.4>	51.70	11.90	51.70	11.90	
Induction IL-2							*0.451*
Yes	81.70	<6.3>	81.70	<6.3>	81.70	<6.3>	
No	70.90	<5.7>	64.30	6.90	56.30	9.60	
DGF							*0.016*
No	89.00	<6.3>	89.00	<6.3>	89.00	<6.3>	
Yes	69.20	<5.7>	64.30	6.90	56.30	9.60	

*Totals vary because of missing data.

SR refers to survival rate

SE refers to standard error

Fig.1

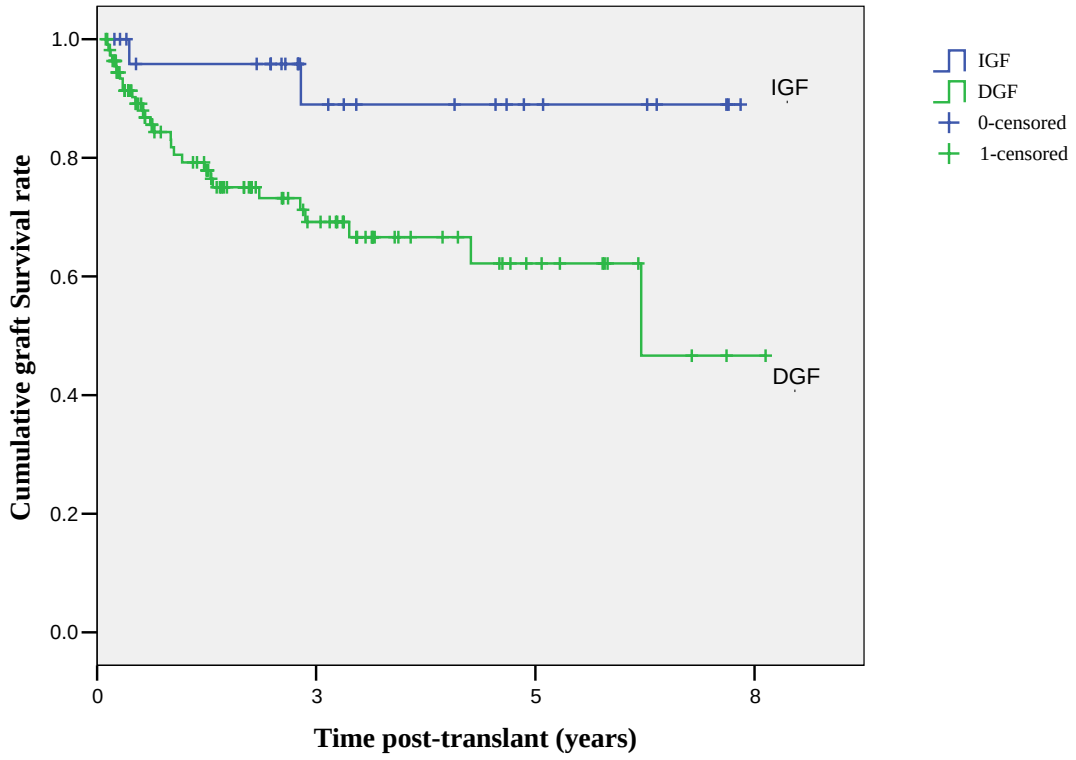

Cumulative graft Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
3
5
8
Time post-translant (years)
IGF
DGF
IGF
DGF
0-censored
1-censored

Fig. 2

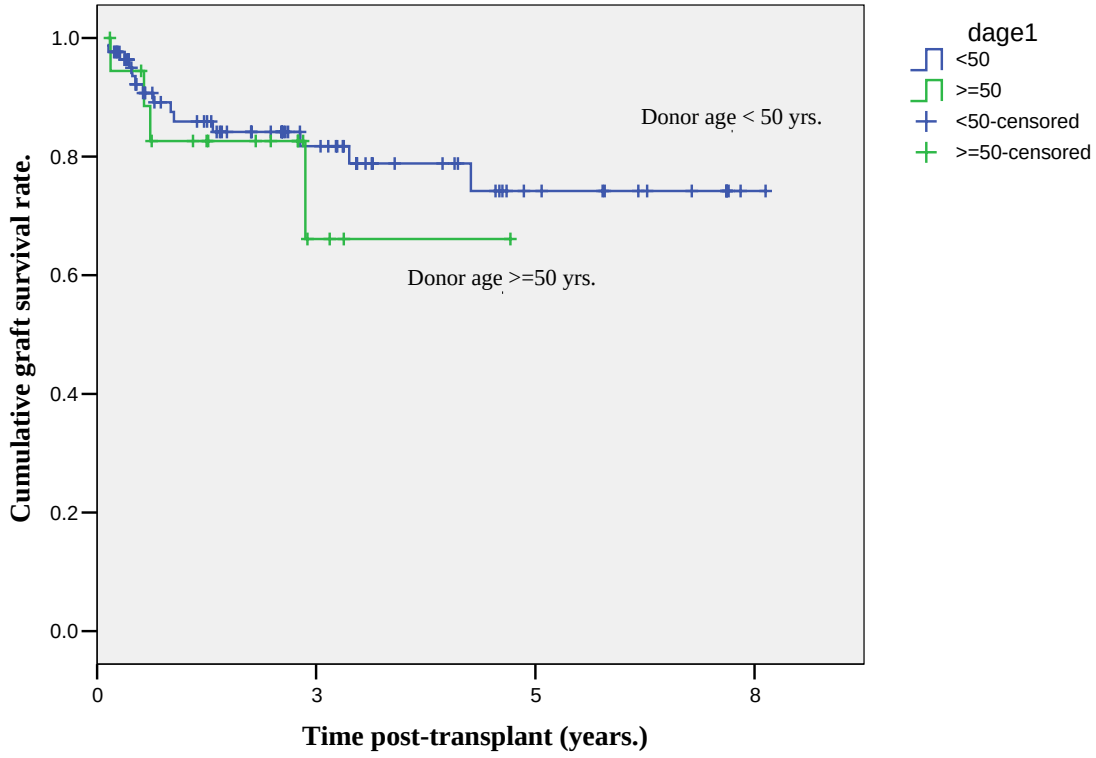

dage1
<50
>=50
<50-censored
>=50-censored
Donor age < 50 yrs.
Donor age >=50 yrs.
Cumulative graft survival rate.
1.0
0.8
0.6
0.4
0.2
0.0
0
3
5
8
Time post-transplant (years.)

Fig. 3

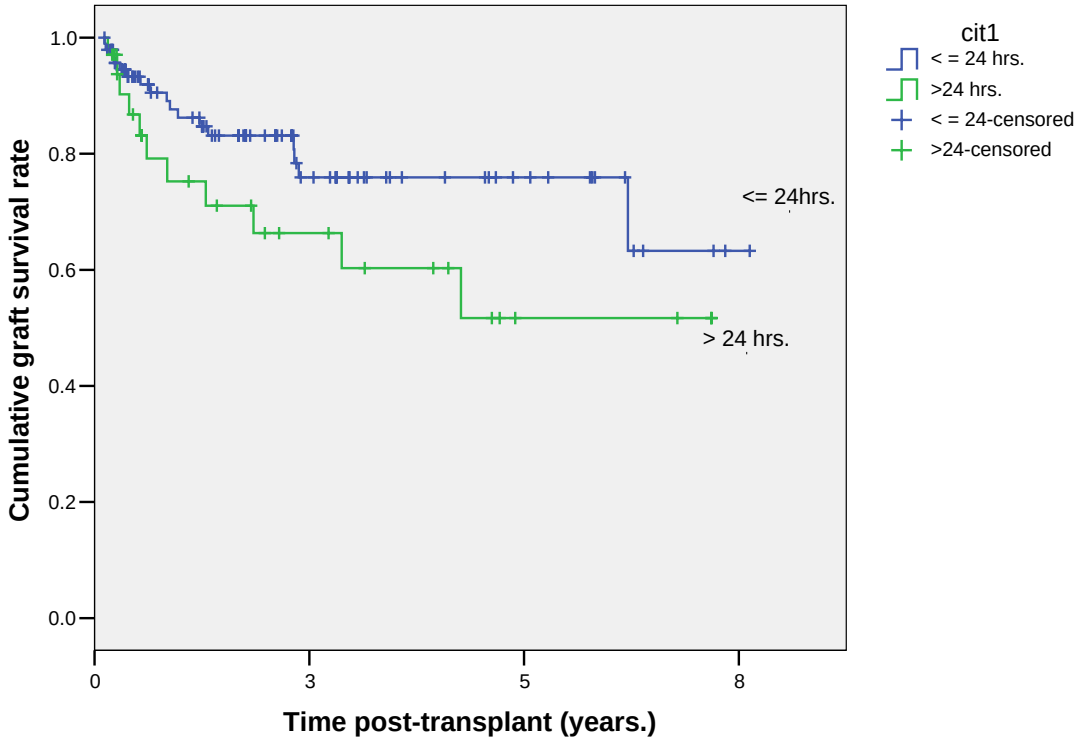
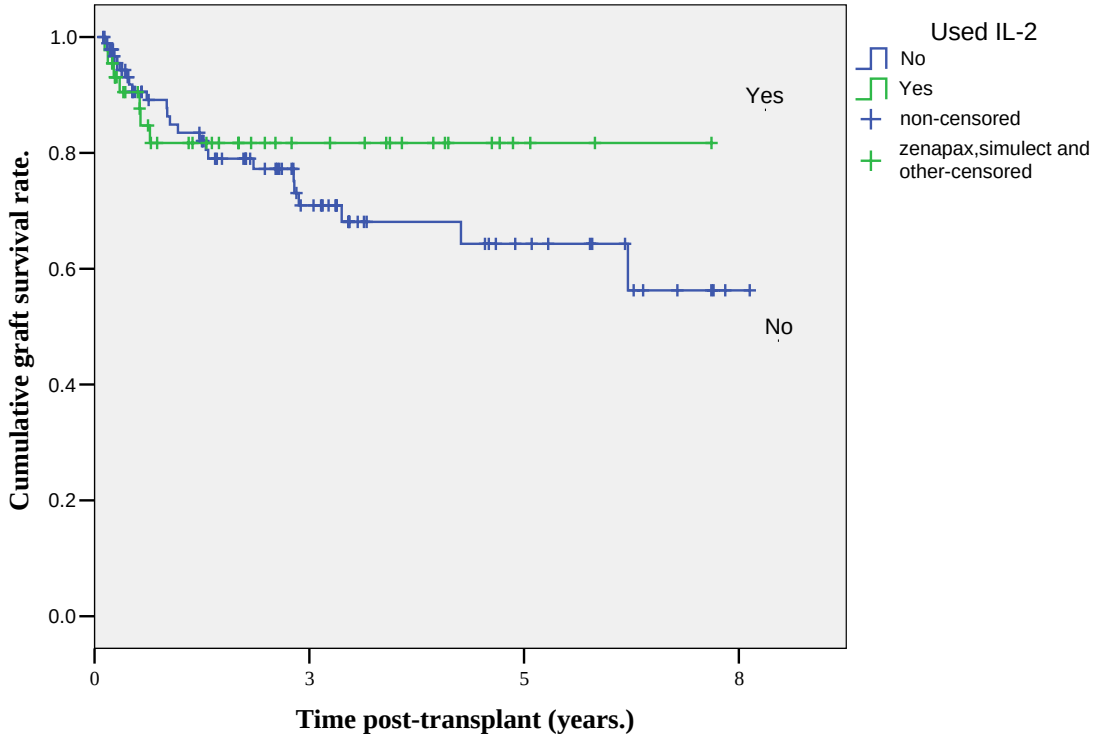

cit1
< = 24 hrs.
>24 hrs.
< = 24-censored
>24-censored
Cumulative graft survival rate
1.0
0.8
0.6
0.4
0.2
0.0
<= 24hrs.
> 24 hrs.
0
3
5
8
Time post-transplant (years.)

Fig. 4


Cumulative graft survival rate.
1.0
0.8
0.6
0.4
0.2
0.0
0
3
5
8
Time post-transplant (years.)
Yes
No
Used IL-2
No
Yes
non-censored
zenapax,simulect and other-censored

4.5 The Cox regression analysis of the transplantation factor

The multivaliate Cox regression was used to analyze the risk factors having p-value <0.200 and induction of IL-2 prior to transplantation for DGF, as shown in Table 4-7. Results showed that the transplantation factors associated between DGF and non DGF. We found higher Hardzard rate (HR) 4.296 (95% CI = 1.004-18.388).

Table 4-7 Multivariate Cox-regression

Valiable	HR	95%CI	*p-value*
Transplantation related.			
Cold ischemia time. *Hours**			
≤ 24 hours.	1		
> 24 hours.	1.785	.825-3.863	*0.141*
Induction IL-2			
Yes	1		
No	1.602	.673-3.813	*0.287*
DGF			
No	1		
Yes	4.296	1.004-18.388	*0.049*

*Totals vary because of missing data.

CHAPTER V
DISCUSSION

5.1 Demographic data of cadaveric kidney transplantion with IGF and DGF

In this retrospective study of 140 cadaveric patients, a number of patients developing IGF and DGF were 19.29% and 81.71%. The IGF occurred when the serum creatinine decrease > 30 % within 48 hrs. post transplantation, while DGF required the need of hemodialysis. The rates of DGF were extremely varied. Mclaren et al. (1999) and Moreso et al. (1999) found the incidence rate of DGF of 27.3% and 29.1% , respectively. Emiroğlu et al. (2005) found that the DGF rates in recipients getting the kidney from cadaveric donor < 50 years and from donor ≥ 50 years were 40% and 46%, respectively. Hetzel et al. (2002) found high occurrence of 44%DGF while Bronzatto et al. (2009) reported 67% of DGF outcome.

In this study, three possible factors causing DGF focused on recipient, donor and transplantation. Though, the multifactors associated with DGF must be taken into consideration to prevent the adverse effect on graft survival. Three aspects of recipients studied were age, gender and duration of dialysis. Compared to two groups of recipients: age < 50 years and ≥ 50 years: the recipient group with age ≥ 50 years showed higher the outcome of DGF than the other group. These results are similar to the study of Friedman et al. (2004) who reported the rate of rejection within the first 90 days was lower only 6.7% of cadaveric recipient over 60 than 37.6% of younger recipients. This could be due to the less immune responses of older recipient. The male gender had higher rate of DGF than female. The impact of longer period of dialysis (> 24 months) also showed high incidence of DGF. Lauzurica et al. (2008) found that the development of DGF was from time of dialysis of 32.78±26.7 months. The types of dialysis (hemodialysis, peritoneal dialysis and predialysis were an independent risk of DGF. This may be the fact that ischemia-reperfusion plays a significant role in DGF from the cause of renal hemodynamics, tubular damage and

inflammation (Lauzurica et al. 2008). The good status of cadaveric kidney donor indicates the possibility of functioning graft. Based on this study, the donor risk factors causing DGF were age > 50 years, male gender, and the death from CVA. Regarding the donor age, the study of Mclaren et al. (1999) and Boom et al. (2000) also reported that donor age > 50 years increased DGF. Verran et al. (2001) reported the DGF rate of 33% in older cadavaric donor over 55 years of age. Oppenheimer et al. (2004) revealed that the increased risk of DGF associated with elder donor (> 60 years). However, in some case of studies, there will be more than one variable affected DGF. Moreso et al. (1999) also reported the increase of DGF was due to the donor age > 50 years and CIT > 26 hours.

The whole process in transplantation includes preservation of kidney during pre-operation, transplantation technique and medication either steroid or antibodies. The well preparation throughout the operation results in better recovery of graft and patient. The transplantation factors studied were cold ischemia time, the matching of HLA, PRA, and induction of IL-2 therapy. The CIT $\geq$ 24 hours, HLA $\geq$ 3 mismatches and PRA > 30%, were dependent risk factors of DGF. The therapy of IL-2 inhibitor prior to operation reduced the risk of DGF.

Based on cold ischemia time (CIT), several studies accepted that CIT > 24 hours showed higher incidence of DGF (McLaren et al. 1999, Browne et al. 2003, Bronzatto et al. 2009). Boom et al. (2000) and Bleyer et al.(1998) reported the patients having CIT> 28 hours displaying DGF. The difference period of CIT was found in the study of Figueiredo et al. (2007) who reported the CIT of more than 22 hours. The short period of kidney preservation is good for kidney healthy status, thereby increasing the graft and patient survival. The reduction in CIT could be performed by a Timesheet which decreased from 21.45 to 13.27 hours (Vacher-Coponat et al. 2007). Hernández et al. (2008) analyzed the 829 kidney transplants recipients from donor < 50 years and found that CIT and death-censored graft loss were independently associated with. However, the loss was increased 20% for every 5 hours of CIT. Based on the study of Peter et al. (1995), the CIT period between 16-40 hours increased the incidence of DGF sharply.

The HLA matching is an immunological indicator prior to transplantation. The effect of HLA typing has been still controversial on the allograft survival.

Vareesangthip et al. (2003) demonstrated that zero AB,DR- mismatched grafts had the highest survival rate. The increased number in mismatch resulted in the reduction of graft survival rate. Lee et al. (2008) also revealed that recipients having zero HLA mismatch and cold ischemia time less than 36 hours improved the 5 –year graft survival period (75%) when compared to the patients with > 1 mismatch HLA.

Panel reactive antibody (PRA) is another essential immunological indicator for renal transplantation. However, a level of PRA varies from one study to another. Arias (2003), Boom et al. (2000) and Bleyer (1998) reported that patients having PRA > 50% had the worst graft survival than those having PRA < 50%.

The use of antibody therapy was targeted to reduce the risk of rejection but to increase the graft survival. Rivera et al. (2005) found that the reduction of DGF was by Basiliximab or Simulect, which is a monoclonal antibody directed toward the alpha chain of the interleukin-2 receptor.

5.2 The univariate and multivariate analysis of the factors affected graft function

In this study, the following variables affected the outcome of transplantation were recipient (age, gender, duration of dialysis before transplantation), donor (age, cause of death) and transplantation (CIT, HLA matching, PRA and induction of IL-2). Univariate and multivariate graft function analysis showed that only the duration of dialysis had significantly impact on the development of DGF and other factors showed trend to impact on the development of DGF but not significantly. These results were similar to the other studies. By using univariate analysis, Moreso et al (1999) reported that the risk factors for DGF were donor age > 50 years (odds ratio (OR) 2.12; 95% CI 1.3-3.45), dual therapy with CsA and steroid OR 2.14; 95% CI 1.37-3.36) and CIT (OR 1.04; 95% CI 1.02-1.07). McLaren et al. (1999) revealed the risk factors for DGF by a multivariate analysis were CIT> 24 hours (OR 2.65; 95% CI 1.8-3.9), PRA > 85% (OR 2.17; 95% CI 1.3-3.5), donor age > 50 years (OR 1.68; 95% CI 1.1-2.6) and pre-emptive transplant (OR 0.132; 95% CI 0.05-0.3). Lauzurica et al (2008) reported that univariate analysis indicated that PAPP-A, TNF-α, cold ischemia, hemodialysis and donor age were risk factors for DGF,

while multivariate analysis showed that only PAPP-A, cold ischemia and hemodialysis were associated with the incidence of DGF.

Hetzel et al (2002) reported that, by multivariate analysis, cold ischemic time was the main risk factor for DGF, whereas donor age and origin of the organ were factors causing DGF by univariate analysis.

Humer et al (2002) analyzed the risk factors for DGF by multivariate analysis. The results showed that donor age > 50 years (relative risk (RR) = 4.1), donor creatinine > 1.7 mg/dl (RR= 1.9), kidney preservation time > 24 hours (RR= 2.7) and recipient PRA > 75% (RR= 3.4).

5.3 The survival analysis of factors associated with DGF

The survival of graft is an ultimate goal for transplantation. However, several factors affected survival must be carefully identified and determined. The study showed that after 7 years of follow-up, patients with DGF had lower in graft survival than those with IGF. However, donor and transplantation were the risk factors for graft and patient survival rate. This study may be similar to the long term clinical study of Hetzel et al (2002) who revealed the patient survival after 7 years. The younger patients tended to have higher percentage of survival than the older patients and the patients with DGF had lower in survival than those with non-DGF.

For the short term study of survival, Pieringer and Biesenbach (2005) reported that the graft survival in the DGF group was lower than the IGF group after 3 years of transplantation. Yarlagadda et al (2008) showed that no significant association of DGF and patient survival at 5 years of follow-up. McLaren et al. (1999) demonstrated that the risk factors for survival by a multivariate analysis were no rejection /no DGF (OR 0.70; 95% CI 0.52-0.95), donor age > 50 years (OR 1.66; 95% CI 1.3-2.2), DGF/ acute rejection (OR 1.54; 95% CI 1.1-2.2) and recipient age > 50 years (OR 1.48; 95% CI 1.1-1.9). Woo et al (1999) confirmed that good renal function during the first three months after transplantation and the absence of acute rejection resulting in long term graft survival. Both univariate and multivariate analyses had no relationship between DGF and long term patient survival. The study also showed that no relationships of recipient age, gender, primary renal disease, time on renal replacement therapy and DGF were associated with graft survival. Oppenheimer et al

(2004) indicated that elderly donor age (≥ 60 years) caused significantly losses of graft and patient. The results also demonstrated that increase in donor age reduces long term patient survival. This may be the healthy status in the elder donor who could develop cardiovascular complication, thereby reducing the progress of graft function.

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5.4 The Cox regression analysis of the transplantation factor

In this study, only the relationship between two variables (CIT and induction of IL-2) and the incidence of DGF were analyzed by the Cox regression,other variables had missing data more than 15% . The analysis revealed that CIT was risk factors for DGF and using induction of IL-2 was reduced risk of DGF and increased GSR. The results were sim fromilar other studies. Moreso et al (1999) showed the results analyzed by multivariate Cox regression supported that donor age and DGF are the two independent predictors of graft survival.

Prommol et al (2000) analyzed the factors affecting graft survival function in 3 different durations, that are ≤ 6 months, 6 months- 5 years and > 5 years by Cox regression univariate analysis. Only donor age ≥ 55 years and female donor had significant effect on long term survival > 5 years.

5.5 Limitations of this study

The study design is a historical cohort, we can not avoid missing data. All multivariable analysis was based on non-missing data.We wonder results might differ if data were not missing. We therefore had applied imputation using a regression method to predict and to replace those missing values of the following the recipients, donors and transplant variables. Fitting the Cox' model using the imputed data came up with a different model.

CHAPTER VI
CONCLUSION AND RECOMMENDATION

This study was conducted on cadaveric kidney transplantation at Siriraj Medical School Hospital, Bangkok, Thailand, starting from January 2002-January 2009. A total number of transplant patients studied were 147. After transplantation, 7 patients were excluded from the analysis due to the non function of graft. Therefore, 140 patients were used to analyze in the study. The risk factors for delayed graft function focused on three following variables including recipient (age, gender, duration of dialysis), donor (age, gender, cause of death) and transplantation related factors (cold ischemia time, HLA mismatch, panel reactive antibody (PRA) and induction of IL-2).

Of 140 patients, 113 patients showed delayed graft function (DGF) (male = 62 (82.7%) and female = 51(78.5%)). Results showed that 86 recipients aged < 50 years and 27 patients aged ≥50 years, respectively. The DGF patients performing dialysis< 24 hours and ≥ 24 hours were 12(66.7%) and 75(89.3%), respectively.

On the cadaveric donor side, two groups of donor aged < 50 and > 50 years were 67 (78.8%) and 6(84.2%) found in DGF. The causes of death of cadaveric donor were 51 (81%) from traffic accident, 15(88.2%) from CVA, 23 (76.7%) from head injury and 24 (80%) from others showed in DGF.

The transplantation factors associated with DGF including CIT <24 hours, CIT ≥ 24 hours, HLA < 3 mismatch, HLA > 3 mismatch, PRA < 30%, PRA≥ 30%, number of patients receiving induction therapy and numbers of patients did not have induction therapy found 76 (79.2%), 29 (85.3%), 50 (78.1%), 51 (81%), 101(81.5%), 12 (75%), 38 (84.4%) and 75 (78.9%), respectively.

Univariate analysis indicated that the recipient risk factor for DGF was only duration of dialysis, not recipient age and gender. However, the donor and transplantation variables were not considered as the risk factors for DGF by univariate

analysis. Based on the multivariate logistic regression, results found that patients performing hemodialysis ≥ 24 months was a significant factor associated with DGF.

After 7 years of follow–up, there was significant difference in graft survival rate between patients with IGF and DGF. The graft survival rate in DGF group was lower than IGF group. The donor aged < 50 years had better graft survival rate compared to the elderly donor aged ≥ 50 years. No significant difference of survival was associated with these two donor age groups. The donor dead from CVA had lower in graft survival rate than other cause of death. No significant difference of survival rate was found among traffic, CVA, head injury and others. CIT, HLA mismatch, PRA and induction of IL-2 did not show significant difference in relation to the graft survival rate. However, the shorter time of CIT < 24 hours showed better survival rate than the other group having CIT ≥24 hours.

The patients with DGF decreased the survival rate of 69.2, 64.3 and 56.3% for 3, 5 and 7 years of follow-up. The difference found that the patients with non-DGF had no effect on the survival rate at the same time of follow-up.

REFERENCES

1. Wolfe RA, Ashby VB,Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999; 341:1725–1730.
2. K. Vareesangthig, P. Jitpraphai, A.Vongwiwatana, P.Permpikul, C. Pornpong, R. Larpkitkachorn, L.Ong-Aj-Yooth, and for the Siriraj Renal Transplantation Working Group.Transplantation Proceedings, 35, 159-162. (2003)
3. Sung RS, Guidinger MK, Christensen LL, et al. Development and current status of ECD kidney transplantation. In: Cecka JM, Terasaki PI, eds. Clinical transplants 2005. Los Angeles:
4. Ojo AO, Hanson JA, Meier-Kriesche H, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol* 2001; 12:589-597.
5. Torregrosa, JV, Campistol, JM, Fenollosa, B, et al. Role of second Hyperparathyroidism in the development of post-transplant acute tubular Necrosis. Nephron 1996; 73:67.
6. Whiting JF, Woodward RS, Zavala EY, et al. Economic cost of expanded criteria donors in cadaveric renal transplantation: analysis of Medicare payments. *Transplantation* 2002;70:755-760.
7. Port, FK, Dykstra, DM, Merion, RM, Wolfe, RA. Trends and results for organ donation and transplantation in the United States, 2004. Am J Transplant 2005; 5:843.
8. 2007 OPTN/SRTR annual report at www.ustransplant.org, accessed 2/09.
9. OPTN/SRTR annual report. www.ustransplant.org, accessed February, 2009.
10. The Organ Procurement and Transplantation Network. http://www. OPTN.org (accessed July 5 2004).

11. Senel FM,Karakayali H, Moray G, Haberal M. Delayed graft function:predictive factors and impact on outcome in living-rdlated kidney transplantations. Ren Jail 1998;20:589-95.

12. William J.C. Amend, Jr., Flavio Vincenti, and Stephen J.Tomlanovich. The first two Posttransplantation months.Gabriel M.Danovitch 2001; 169-170

13. McKay DB, Milfrd EL, Sayegh MH.Clinical aspects of renal Transplantation. In:Brenner BM, Rector FC, editors.The Kidney, 5th ed.Philadephia: Saunders; 1995.

14. Kasiske BL, Ramos EL, Gaston RS, Bia MJ, Danovitch GM, Bowen PA, et al. The evaluation of renal transplant candidates: clinical practice guidelines.Patient Care and Education Committee of the American Society of Transplant Physicians. J Am Soc Nephol 1995;6(1):1-34.

15. AO, Wolfe RA, Held PJ, et al: Delayed graft function: risk factors and implications for renal allograft survival. Transplantation 63:968, 1997.

16. Lim, EC, Terasaki, PI. Early graft function. In: Clinical Transplants, Terasaki, PI (Ed), UCLA Tissue Typing Laboratory, Los Angeles, 1991, p. 401.

17. Irish, WD, McCollum,DA, Tesi, RJ, Owen, AB. Nomogram for predicting the likehoodOf delayed graft function in adult cadaveric renal tranlplant recipients. J Am Soc Nephrol 2003; 14:2967.

18. Weiss A, Littman DR, signal transduction by lymphocyte antigen receptors. Cell1994;76(2):263-74.

19. Belzer F, Salvatierra O. Renal transplantation: organ procurement, preseration, and surgical management, In: Brenner BM, Rector FC, editors.The Kidney. Philadephia: W.B. Saunder; 1976.p. 1796-1818.

20. krensky AM, Weiss A, Crabtree G, Davis MM. Parham P.T-lymphocyte- antigen interactions in transplant N Engl J Med 1990;322(8):510-7

21. Belzer F, Salvatierra O. Renal transplantation: organ procurement, preseration, and surgical management, In: Brenner BM, Rector FC, Editors.The Kidney. Philadephia: W.B. Saunder; 1976.p. 1796-1818.

22. McKay DB, Milfrd EL, Sayegh MH. Clinical aspects of renal transplantation.In: Brenner BM, Rector FC, editors. The Kidney, 5th ed.Philadephia: Saunders; 1995.23. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976.

24. Karl L.Womer, Herwig-Ulf Meier-Kriesche, Bruce Kaplan.Graft and Patient Survival. *Medical Management of Kidney transplantation* 2005; 1:7. 2005;235.

25. Henk Boom, Leendert C. Paul, Johan W. de Fijter.Delayed graft Function in renal transplantation.*Transplantation Reviews 2004 ;18;3: 139-152*.

26. Moreso F, Seron D, Gilvernet S et al. Donor age and delayed graft function as predictors of renal allograft survival in rejection-free patients. Nephrol Dialysis Transplant 1999:14: 930-935.

27. Mandelbrot, DA, Pavlakis, M, Danovitch, GM, et al. The medical evaluation of living Kidney donors: a survey of US transplant centers.Am J Transplant 2007; 7:2333.

28. Baylis C, Schmidt R.The aging glomerulus. Semin Nephrol 1996:16: 265-276.

29. Anderson S, Brenner BM. Effects of aging on the renal glomerulus. Am J Med 1986:80:435-442.

30. Kappel B, Olsen S. Cortical interstitial tissue and sclerosed glomeruli in the normal human kidney, related to age and sex. A quantitative study. Virchows Arch A Pathol Anat Histol 1980:387: 271-277.

31. Nyengaard JR, Bendtsen TF.Glomerular number and size in relation to age, kidney weight, and body surface in normal man. Anat Rec1992:232: 194-201.heartbeating 'brain dead'organ donor.JAMA1989:261: 2222-2228.

32. Elizabeth Kendrick, Jennifer Singer, H. Albin Gritsch, and J. Thomas Rosenthal.Medical and Surgical Aspects of Kidney Donation. Handbook of Kidney Transplatation 2005; p165.

33. Peters ThG. Shaver TR, Ames JE, Santiago-Delpin EA, Jones KW, Blanton JW. Cold ischemia and outcome in 17.937 cadaveric kidney transplants. Transpl Immunol1995:59: 191-196.

34. Neumayer H.H., Eis M., Link J., Muhlberg J., Wagner K. Factors influencing Primary Kidney Graft Function.Transplant Proc 1986: XVIII: 1013-1117.

35. Schmidt R., Kupin W., Dumler F., Venkat K.K., Mozes M. Influence of the Pretransplant Hematocrit level on Early Graft Function in Primary Cadaveric Renal Transplantation.Transplantation 1993:55:

36. Kahan B., Mickey R., Flechner S.M. et al. Multivariate Analysis of risk Factors Impacting on Immediate and Eventual Cadaver Allograft Survival in Cyclosporine-Treated Recipients.Transplantation 1987:43:65-70.

37. Belli L.S., De Carlis L., Del Favero E. et al. The role of donor and recipient factors in initial renal graft nonfunction.Transplant Proc1988: XX: 861-864.

38. Koning OHJ, Ploeg RJ, van Bockel JH et al. Risk factors for delayed graft function in cadaveric kidney transplantation - A prospective study of renalfunction and graft survival after preservation with University of Wisconsin solution in multi-organ donors.Transplantation 1997:63: 1620-1628.

39. Pfaff WW, Howard RJ, Patton PR, Adams VR, Rosen CB, Reed AI. Delayed graft function after renal transplantation.Transplantation 1998:65: 219-223.

40. Gerd Rudiger Hetzel ,Barbara Klein ,Matthias Brause,AndreasWesthoff,Reinhart Willers,Wilhelm Sandmann, Bernd Grabensee.Risk factors for delayed graft Function after renal transplantation and their significance for long-term clinical outcome ; Transpl Int (2002) 15:10-16.

41. Ojo AO, Wolfe RA, Held PhJ, Port FK, Schmouder RL. Delayed graft function: risk factors and Implications for renal allograft survival Transplantation 1997:63:968-974.

42. Matas AJ, Gillingham KJ, Elick BA et al. Risk factors for prolonged hospitalization after kidney transplants.Clin Transplant 1997:11:259-264.

43. Neumayer HH, Kunzendorf U, Schreiber M. Protective effects of calciumantagonists in human renal transplantation. Kidney Int Suppl 1992:36:S87-93.: S87-S93.

44. Es v.A., Hermans J., Bockel v.H.J., Persijn G.G., Hooff J.P., Graeff J.de. Effect of Warm Ischemia Time and HLA (A en B) matching on renal cadaveric graft survival and rejection episodes. Transplantation 1983:36: 255-258.

45. Daemen JW, Kootstra G, Wijnen RM, Yin M, Heineman E.Nonheart-beatingdonors: the Maastricht experience. Clin Transpl 1994:303-316.1034-1040.

46. Denton MD, Magee CC, Sayegh MH. Immunosuppressive strategies intransplantation. Lancet 1999; 353(9158):1083-91.

47. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J AmSoc Nephol2000;11(10):1910-7.

48. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C.Mycophenolate mofetil in enal allograft recipients:a pooled efficacy Analysis of three randomized, double-blind, clinical studies in Prevention of rejection.The International Mycophenolate Mofitil Renal Transplant Study Group.Transplantation 1997; 63(1):39-47.

49. A randomized clinical trail of cyclosporine in cadaveric renal transplantation. Analysis at three years. The Canadian Multicentre Transplant Study Group. N Engl J Med 1986; 314(19):1219-25.

50. Ponticelli C, Minetti L, Di Palo FQ, Vegeto A,Belli L, Corbetta G, et al. The Milan clinical trial with cyclosporine in cadaveric renal transplantation a three-year follow-up. Transplantation 1988; 45(5):908-13.

51. Isoniemi HM, Ahonen J,Tikkannen MJ, von Willebrand EQ, Krogerus L, Eklund BH, et al. Long-term consequences of different immunosuppressive Regimens for renal allografts. Transplantation 1993;55(3):494-9.

52. Sonoda T, Takahara S, Takahashi K, Uchida K, Ohshima S, Toma H, et al. Outcome of 3 years of immunosuppression with tacrolimus in more than 1,000 renal transplant recipients in japan. Transplan tation2003; 75(2):199-204.

53. Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, etal.Multicenter randomized trail comparing tracroimus(FK506)and Cyclosporine in the prevention of renal 3 allograft rejection: a report Of the European Tacrolimus Milticenter Renal StudyGroup.Transplantation 1997; 64(3):436-43.

54. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Fillo RS. A comparision oftacrolimus (FK506) and cyclosporine for immunosuppression afte cadaveric renal transplant. FK506 Kidney Transplant Study Group.Transplantation 1997; 63(7):977-83.

55. Liu J, Farmer JD, Jr., Lane WS, Friedman J, Weissman I, Schreiber SL.Calcineurin is a common target of cyclophilin-cyclosporine A and FKBP-FK506 complexes. Cell 1991; 66(4):807-15.

56.Shoskes DA, Wood KJ. Indirect presentation of MHC antigens in transplantation. Immunol 1991;15(1):32-8.UCLA Immunogenetics Center; 2006:37_55.

57.Miceli MC, Paranes JR the roles of CD4 and CD8 in T cell activation. Semin Immunol 1991;3(3):133-41.

58. Nishizuka Y.Intracellular signaling by hydrolysis of phospholipids and activation of protein kinase C. Science 1992;258(5082):607-14.

59. Schwart RH. T cell anergy. Sci Am 1993; 269(2):62-3, 66-71.

60. Clark EA, Ledbetter JA. How B and T cells talk to each other. Nature 1994:367(6462):425-8.

61. Shibuya H, Yoneyama M, Ninomita-Tsuji J, Matasumoto K, Taniguchi T. IL-2 and EGF receptors stimulate the hematopoietic cell cycle via different signaling pathways: demonstration of a novel role for c-myc. Cell 1992;70(1):57-67.

62. Strom TB, Tilney NL, Carpenter CB, Busch GJ. Identity and cytotoxic capacity of cells infiltrating renal allografts. N Engl J Med 1975; 292(24): 1257 –63.

63. Klasusner RD, Samelson LE. T cell antigen receptor activation pathways: the tyrosine kinase connection Cell 1991;64(5):857-8.

64. Norberto Perico, Dario Cattaneo, Mohamed H Sayegh, Giuseppe Remuzzi. Delayed graft function in kidney transplantation. http://www.thdlancet.com Vol 364 November 13, 2004.

65. Meena Sahadevan and Bertram L. Kasiske. Long-Term Posttransplant Management and Complications,Handbook of Kidney transplantion

66. Halloran PF, Hunsicker LG: Delayed graft function: state of the art, November 10–11, 2000. Summit meeting, Scottsdale, Arizona, USA. Am J Transplant.1:115, 2001.

67. Shoskes DA, Shahed AR, Kim S: Delayed graft function. Influence on outcome and strategies for prevention. Urol Clin North Am 28:721, 2001.

68. AZIZ WALELE, MBCHB, MMED, FCP (SA) AND CARL J. CARDELLA, MD, FRCPC. Delayed graft function:Understanding the challenge; NEPHOLOGY Rounds October 2002

69. M.A. Gentil, M.P. Alcaide, G.R. Algarra,P.Pereira, J. Toro, F. Gonzalez-Roncero, M. Lopez, G. Bernal, and J. Mateos. Impact of Delayed Graft Function on Cadaveric Kidney Transplant Outcome. Transplantation Proceedings, 35,689-691(2003)

70. Rosengard BR, Feng S, Alfrey EJ, ey al. Report of the Crystal City miiting to maximize the use of organs recovered from the cadaver donor. *Am J Transplantation* 2002;2:701-711.

APPENDICES

APPENDIX A

Data Record Form

Part 1 Recipient and transplant form

Patient No. (1) KT No. (2) เพศ. (3) อายุ (4) ส่วนสูง(cm.) (5) น้ำหนัก (Kg.) (6)

สาเหตุไตวาย(7) การรักษาก่อนเปลี่ยนไต (8) ระยะเวลาการทำ HD (moth.) (9) Blood Gr. (10)

วันเดือนปีที่เปลี่ยนไต (11) PRA-last (12) CIT (13) ชั่วโมง WIT (14) นาที

HLA matching (15) HLA-A mismatch (16)

HLA-B mismatch (17) HLA-DR mismatch (18)

Induction (19); Yes ☐ No ☐

If yes; Simulect ☐ Zenapax ☐ Other ☐

Initial Immunosuppressive (20)**:**

Cyclosporin ☐ Tacrolimus ☐ Prednisolone ☐ MMF ☐ Myfortic ☐ Other ☐

ได้รับการฟอกเลือดสัปดาห์แรกหลังการผ่าตัด (21) จำนวน ครั้งของการฟอกเลือดหลังผ่าตัด (22)

Yes ☐ No ☐

Best Cr (23) mg/dl Date of best Cr (24) Discharge Cr (25) mg/dl Date of Discharge (26)

Complication หลังผ่าตัด (27): ☐ ไม่มี ☐ มี ถ้ามีระบุ……

Appendix A: คู่มือการเก็บข้อมูล โครงการวิจัย

Part 1 Recipient and transplant form

1) ใส่เลขลำดับที่ของผู้ป่วย
2) ใส่เลขที่ KT ของ recipient
3) เพศของผู้รับปลูกถ่ายไต 1 = ชาย 2 = หญิง
4) อายุของ recipient
5) ส่วนสูงก่อนผ่าตัด ของ recipient หน่วยเป็น cm.
6) น้ำหนักแห้งก่อนผ่าตัด ของ recipient หน่วยเป็น kg.
7) สาเหตุของไตวาย
8) การรักษาก่อนเปลี่ยนไต 1 = HD, 2 = CAPD, 3 = Pre-emptive, 9 = missing
9) ระยะเวลาการฟอกไต (เดือน)
10) กรุ๊ปเลือดของ recipient ใส่เป็น
    Code
    1 = A 2 = B 3 = AB 4 = O 9 = missing
11) วันเดือนปี ของ การผ่าตัดเปลี่ยนไต (ปีเป็น คศ.)
12) ค่า PRA ครั้งล่าสุดใส่เป็น % ถ้าไม่มีข้อมูลให้ใส่ 999
13) ระยะเวลา Cold ischemic time (CIT) ใช้เป็นจำนวนชั่วโมง
14) ระยะเวลา Warm ischemic time (WIT) ใช้เป็นจำนวนนาที
15) ชนิดของ HLA matching
    Code
    1 = HLA Identical 2 = One haplotype 3 = Missmatch
    9 = missing
16) จำนวน HLA-A mismatch ใส่เป็นตัวเลข 0,1,2,3
17) จำนวน HLA-B mismatch ใส่เป็นตัวเลข 0,1,2,3
18) จำนวน HLA-DR mismatch ใส่เป็นตัวเลข 0,1,2,3
19) ใช้ Induction หรือไม่ ถ้าใช้ บอกรายละเอียดตาม code
    1 = yes 2 = No 9 = missing

    If yes specify

    1 = Zenapax 2 = Simulect

20) ยา **Immunosuppressive** ที่ผู้ป่วยได้รับ ณ.วันที่ จำหน่าย

21) การได้รับการฟอกเลือดภายใน 1 สัปดาห์แรกหลังผ่าตัด

0 = No 1 = yes

22) จำนวน ครั้งของการฟอกเลือดหลังผ่าตัด ให้ระบุเป็นตัวเลขจำนวนครั้ง

23) ใส่ค่าระดับ serum creatinine ที่ดีที่สุด (ต่ำที่สุดในการ admission ที่ทำการปลูกถ่ายไต) หน่วยเป็น mg/dL

24) ใส่วันที่ของค่า serum creatinine ที่ดีที่สุด (ปีเป็น คศ.)

25) ใส่ค่าระดับ serum creatinine ของวันที่จะกลับบ้าน หรือ 1 วันก่อนกลับบ้าน

26) ใส่วันที่ผู้ป่วยจำหน่ายกลับบ้าน (ปีเป็น คศ.)

27) ใส่ภาวะแทรกซ้อนหลังการผ่าตัด

0 = ไม่มี 1 = มี

ถ้ามีระบุชื่อภาวะแทรกซ้อน พร้อมวันที่ (ปีเป็น คศ.)

APPENDIX B

Data Record Form

Part 2 Donor form

KTNO. of recipient (1) เพศ (2) อายุ (3) Blood Gr. (4) HN. Of recipient (5)

สาเหตุการเสียชีวิต (6) การรักษาก่อนเสียชีวิต (7) HLA matching(8)

HLA-A mismatch(9) HLA-B mismatch (10) HLA-DR(11) mismatch

Lest Cr(12)
mg/dl

Part 2 Donor form

1) ใส่เลข KT ของ recipient
2) เพศของผู้บริจาคไต 1 = ชาย 2 = หญิง 3 = Missing
3) อายุขณะบริจาคไตให้ใส่เป็นจำนวนปี
4) กรุ๊ปเลือดใส่เป็น
   Code
   1 = A 2 = B 3 = AB 4 = O 9 = Missing
5) HN ของผู้รับไต (recipient)
6) สาเหตุของการเสียชีวิต ให้ระบุ
7) การรักษาก่อนเสียชีวิต ให้ระบุ
8) ชนิดของ HLA matching
   Code
   1 = HLA Identical 2 = One haplotype 3 = Missmatch
   9 = missing
9) จำนวน HLA-A mismatch ใส่เป็นตัวเลข 0,1,2,3
10) จำนวน HLA-B mismatchใส่เป็นตัวเลข 0,1,2,3
11) จำนวน HLA-DR mismatchใส่เป็นตัวเลข 0,1,2,3
12) ใส่ค่าระดับ serum creatinine สุดท้ายก่อนผ่าตัดไต

APPENDIX C

Data Record Form
Part 3 Data Follow up Record Form

Visit (16) …..

Hospital No. (1) ☐☐☐ KT No. (2) ☐ เพศ (3) ☐ อายุ (4) ☐☐ ส่วนสูง (cm.) (5) ☐☐☐ น้ำหนัก (kg.) (6) ☐☐☐

Date of visit (7) ☐☐☐☐☐☐ SBP (8) ☐☐☐ DBP (9) ☐☐☐ Serum C r(10) ☐☐☐ mg/dl

Graft out come(11) ☐ ยังทำงานอยู่ ☐ ไตเสียแล้ว ; สาเหตุ ☐ ☐ Loss follow up

Patient status(12) ☐ ยังมีชีวิตอยู่ ☐ เสียชีวิตแล้ว ☐ Loss follow up

วันที่เสียชีวิต(13) ☐☐☐☐☐☐ สาเหตุ……

Last follow up (14) ☐☐☐☐☐☐

Complication(15) : ☐ ไม่มี ☐ มี ถ้ามีให้ระบุ……..

Part 3 Data Follow up Record Form

1) ใส่เลขประจำตัวโรงพยาบาล(HN)ของผู้ป่วย
2) ใส่เลขที่ KT ของ recipient
3) เพศของผู้รับปลูกถ่ายไต 1 = ชาย 2 = หญิง
4) อายุของ recipient
5) ส่วนสูงของ recipient หน่วยเป็น cm.
6) น้ำหนัก ณ วันที่มาตรวจของ recipient หน่วยเป็น kg.
7) วันเดือนปี ที่ follow up (ปีเป็น คศ.)
8) ใส่เลขความดันโลหิตตัวบน ถ้าไม่มีข้อมูลให้ใส่ 999
9) ใส่เลขความดันโลหิตตัวล่าง ถ้าไม่มีข้อมูลให้ใส่ 999
10) ระดับ creatinine ในเลือด ถ้าไม่มีข้อมูลให้ใส่ 999
11) สถานะของไต ณ วันที่ Follow up ว่ายังทำงานอยู่หรือไม่

Code

1 = ยังทำงานอยู่ 2 = ไตเสียแล้ว 9 = Loss follow up

ถ้าไตเสียแล้วให้ลงสาเหตุดังนี้

Code 1. Acute rejection
2. Chronic rejection
3. CSA nephrotoxicity
4. Renal artery sternosis
5. Other……..

12) สถานะของผู้ป่วย ณ วันที่มา Follow up ว่ายังมีชีวิตอยู่หรือไม่

Code

0 = เสียชีวิตแล้ว 1 = ยังมีชีวิตอยู่ 9 = Lost follow up

13) ถ้าเสียชีวิตให้ระบุวันที่เสียชีวิต พร้อมระบุสาเหตุ……
14) ให้ลงวันที่มา Follow up ครั้งสุดท้าย (ปีเป็น คศ.)
15) ใส่ภาวะแทรกซ้อน

0 = ไม่มี 1 = มี ถ้ามีระบุภาวะแทรกซ้อน……

16) ลงครั้งของการมา Follow up

Code

1 = 6 เดือน 2 = 1 ปี 3 = 2ปี 4 = 5ปี

BIOGRAPHY

NAME	Miss.Sukgunya Piakhummueang
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