Post-transplant hypertension after kidney transplantation

List of abbreviations

ABPM:	Ambulatory blood pressure monitoring
ACC:	American College of Cardiology
AHA:	American Heart Association
BMI:	Body mass index
BP:	Blood pressure
CAI:	Chronic allograft injury
CIT:	Cold ischemia time
CNI:	Calcineurin inhibitor
CsA:	Cyclosporine A
DBP:	Diastolic blood pressure
DGF:	Delayed graft function
eGFR:	Estimated glomerular filtration rate
ESC:	European Society of Cardiology
ESH:	European Society of Hypertension
HBPM:	Home blood pressure monitoring
HDL:	High-density lipoprotein
HLA:	Human leucocyte antigen
HT:	Hypertension
JNC:	Joint National Committee
KTR:	Kidney transplant recipients
KTx:	Kidney transplantation
LBW:	Low birth weight
LDL:	Low-density lipoprotein
MMF:	Mycophenolate mofetil

MFA: Mycophenolic acid

mTOR: Mammalian target of rapamycin

PTH: Parathyroid hormone

RAAS: Renin-angiotensin-aldosterone system

SBP: Systolic blood pressure

Tac: Tacrolimus

TRAS: Transplant renal artery stenosis

UA: Uric acid

UCR: Urine protein-creatinine ratio

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1 Introduction

1.1 Definition of hypertension in general population and kidney transplant recipients

In terms of defining hypertension (HT), there are several guidelines currently available. Among them, the following three guidelines are most commonly used:

European Society of Cardiology/European society of Hypertension (ESC/ESH) (Williams *et al*, 2018);

Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC) (Chobanian *et al*, 2003) and

American College of Cardiology/American Heart Association (ACC/AHA) (Whelton *et al*, 2017)

According to the 2018 ESC/ESH guidelines, HT was defined as systolic blood pressure (SBP)≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg in general population. Similarly, JNC-7 diagnosed HT as SBP≥140 mmHg and/or DBP≥90 mmHg or the need for antihypertensive therapy. However, JNC-8 did not address the threshold for HT (James *et al*, 2014). In contrast, recent 2017 ACC/AHA guidelines recommend 130 mmHg and 90 mmHg as cutoff values for SBP and DBP, respectively. Table 1.1 compares current BP thresholds according to these guidelines.

In the case of kidney transplantation (KTx), much uncertainty still exists about the relationship between blood pressure (BP) level and outcomes in kidney transplant recipients (KTR). As a result, there has been little agreement about the definition of HT in this group.

1.2 Epidemiology of hypertension after kidney transplantation

HT after KTx has been identified as an important risk factor for chronic allograft dysfunction. The prevalence and incidence of HT after renal transplantation varies among different studies. Here are some possible explanations:

A generally accepted definition of HT after KTx is lacking;

The published scientific articles differ in terms of their populations and study designs;

The introduction of newer immunosuppressive drugs following the 1980s, namely calcineurin inhibitors (CNI) and

Table 1.1: Definition of hypertension according to the different guidelines

Definition of HT according to ESC guidelines			
	SBP		**DBP**
Office	140	And/or	90
HBPM	135	And/or	85
ABPM			
Daytime	135	And/or	85
Nighttime	120	And/or	70
24-Hour	130	And/or	80
Definition of HT according to ACC guidelines			
Office	130	And/or	80
HBPM	130	And/or	80
ABPM			
Daytime	130	And/or	80
Nighttime	110	And/or	65
24-Hour	125	And/or	75
Definition of HT according to JNC-7 guidelines			
Office	140	And/or	90
HBPM	No formal thresholds		No formal thresholds
ABPM			
Daytime	No formal thresholds		No formal thresholds
Nighttime	No formal thresholds		No formal thresholds
24-Hour	No formal thresholds		No formal thresholds

SBP, systolic blood pressure; DBP, diastolic blood pressure; HBPM, home blood pressure monitoring; ABPM, ambulatory blood pressure monitoring

The measurements of BP (i.e., out-of-office or office monitoring) which set different cutoff values for HT.

As an example, Pérez Fontan *et al*. (1999) assessed 680 renal transplant recipients receiving cyclosporine (CsA) immunosuppression. It turned out that the prevalence of HT was about 78% at the end of first year. In another study of 3365 adult kidney recipients, the prevalence of HT was 80% at 3 years or more and 85% at year five after KTx (Campistol *et al*, 2004). Overall, in adults, prevalence of HT after KTx is estimated to be 70-90%, while in children, it ranges from 58-89% (Charnaya and Moudgil, 2017).

1.3 Classification of hypertension in kidney transplant recipients

KTR can be categorized into 4 groups based on their BP profile (Malek-Hosseini *et al*, 1998; Tantisattamo *et al*, 2020):

1. Persistent HT: Patients with HT both before and after KTx

2. Recovered HT: Patients with HT only before KTx

3. Post-transplant HT: Patients who develop HT only after KTx

4. Persistent normotension: Patients without history of HT and they remain normotensive after KTx.

1.4 Assessment of hypertension in kidney transplant recipients

BP assessment in kidney recipients can be carried out through office blood pressure measurements, ambulatory blood pressure monitoring (AMBP) and home blood pressure monitoring (HBPM). Several clinically useful groups of HT can be differentiated using noninvasive BP monitoring techniques, depending on where the measurement takes place. (Figure 1-1)

In a recent study by Korogiannou *et al*. (2021), the prevalence of HT in KTRs by office BP was 88.3% using ESC/ESH guidelines and 92.7% using ACC/AHA definitions. However, when ABPM was used, the prevalence of HT was reported to be 94.1% and 98.5% at relevant thresholds, respectively.

An important question, however, is which methods of measurement is more efficient, cost-effective and accurate. In a study comparing HBPM and office BP monitoring among transplant recipients, HBPM correlated better with both SBP and DBP levels. Moreover, HBPM showed better agreement with ABPM (Agena *et al*, 2011). A recent systematic review and meta-analysis compared office BP measurements with ABPM,

revealing that office BP measurements were associated with a high proportion of masked HT and uncontrolled HT (Pisano *et al*, 2022).
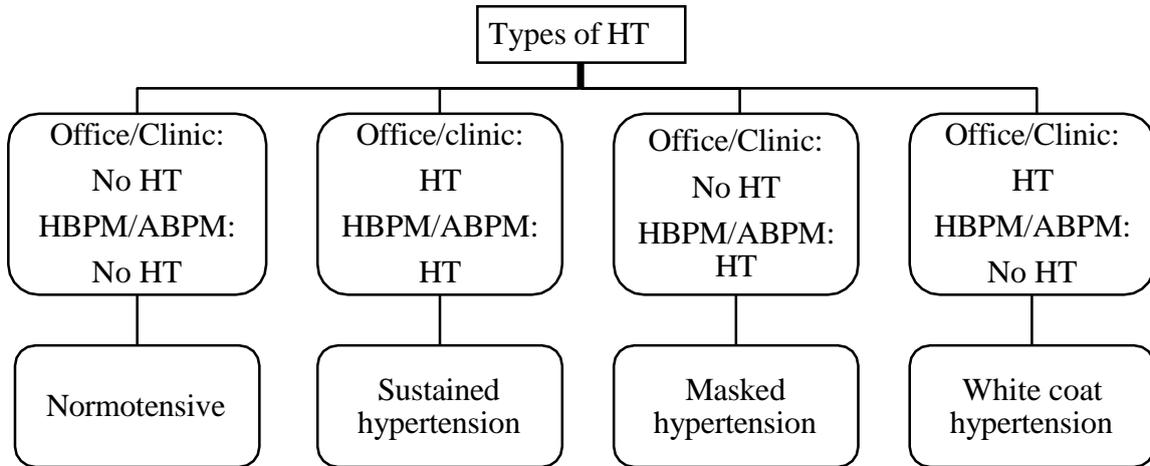
Figure 1-1. Types of hypertension based on office and out-of-office measurements

In conclusion, the results of ABPM differ substantially from those obtained at the office. Therefore, the poor performance of office BP monitoring makes ABPM and HBPM the preferred options to confirm the diagnosis of HT in KTR.

1.5   Pathogenesis of post-transplant hypertension

Donor and recipient factors play crucial role in the development of HT after KTx. These includes:

1.5.1   Donor-related factors

1.5.1.1   Low nephron mass

In 1988, Brenner *et al*. on the basis of their hyper-filtration hypothesis, suggested that renal mass reduction leads to glomerular alterations that may lead to long term health problems. According to this hypothesis, as the number of nephrons decline, the capacity to excrete sodium is decreased, which make people more susceptible to HT. A vicious cycle will eventually develop, leading to kidney failure over time (Figure 1-2).

Maternal factors	Genetic polymorphism
Maternal nutrition	PAX2
Low protein diet	RET
Vitamin A deficiency	OSR1
Iron deficiency	ACE
Maternal Behaviors	BMPR1A
Smoking	Combined RET polymorphism and PAX2 haplotype
Alcohol consumption	Combined OSR1 and RET polymorphisms
Substance abuse	Combined OSR1 and PAX2 polymorphisms
Disorders of the mother	
Pre-eclampsia	
Hypertension	
Medications	

↓ Nephron number

Glomerular hypertension and eventually glomerular sclerosis

↓ Filtration surface area

↑ Mean arterial BP
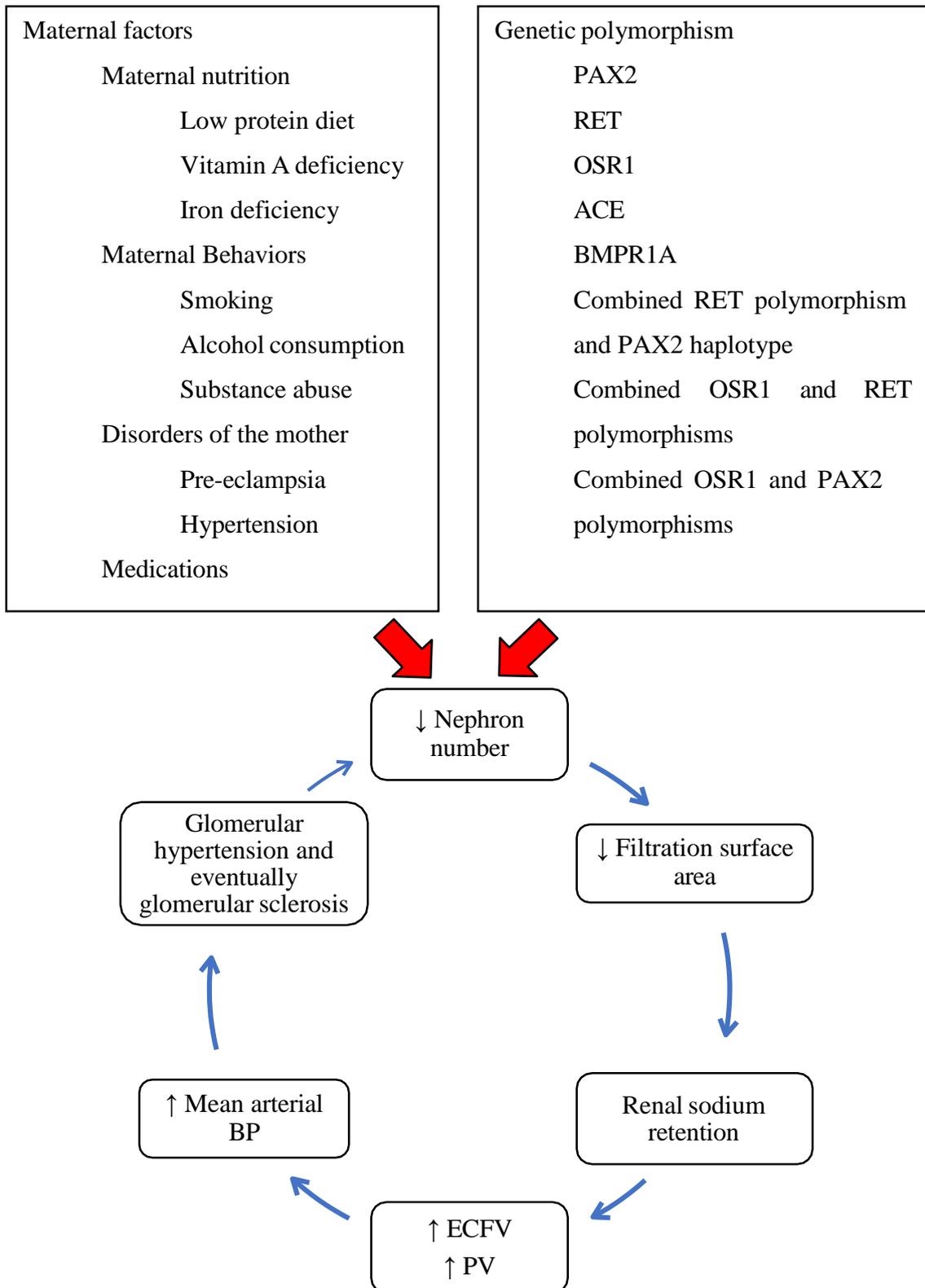
Renal sodium retention

↑ ECFV
↑ PV

Figure 1-2. Causes of low nephron number and its clinical consequences

PAX2, paired box gene; RET, tyrosine kinase receptor; OSR, Odd-Skipped related; ACE, angiotensin-converting enzyme; BMPRA, bone morphogenic protein receptor; ECFV, extracellular fluid volume; PV, plasma volume (Brenner *et al*, 1988; Luyckx *et al*, 2013).

Several surrogate markers are suggested for determining the nephron number. These includes: low birth weight (LBW), premature birth, short stature, female gender, ethnicity, glomerular volume and kidney volume on ultrasound (Luyckx *et al*, 2011; Luyckx and Brenner, 2010). Thus far, the most useful clinical surrogate for low nephron number is LBW (defined as birth weight <2.5 kg) (Luyckx *et al*, 2013). The discovery that lower birth weight is linked to higher BP has been confirmed in numerous studies. Although much research has been done in this field, the exact nature of the relationship between birth weight and BP is still debated.

A systematic review conducted by Huxley *et al*. (2002) revealed that birth weight was not a significant factor in predicting BP in later life. Later, a study of 25874 men and women between the ages of 17 and 64 found that higher adult SBP was predicted by lower birth weight (Davies *et al*, 2006). Similarly, another meta-analysis which assessed 5 studies, concluded that LBW was associated with 30% increased risk of HT compared with birth weight ≥2.5 kg (Odds ratio:1.30, 95% CI: 1.16-1.46) (Knop *et al*, 2018).

Regarding KTx, few studies have conducted in order to examine the relationship between LBW of donor and post-transplant HT. In a study of 91 donor-recipient pairs, it was shown that recipients of donors with LBW took a considerably higher number of antihypertensive medications (SchacHTer and Reinke, 2017). The same authors demonstrated in a similar study that living donors with birth weight ≤2.5 kg developed proteinuria and HT significantly more than those with birth weight>2.5 kg (SchacHTer and Reinke, 2016).

In summary, it is conceivable that a decreased number of donor nephrons, due to any reasons, could play a significant role in chronic graft failure and HT by failing to meet the metabolic needs of recipients.

1.5.1.2 Age, Gender and BMI

Patients receiving older donor kidneys tend to have higher BP than those receiving younger donor kidneys (Cosio *et al*, 2003; Campistol *et al*, 2004). This can be explained by fewer functioning glomeruli in older kidney donors (>55 years) compared to younger ones (Tan *et al*, 2010).

Uncertainty exists regarding the importance of donor gender in the development of arterial HT following KTx. As an example, recipients who received kidneys from female donors had a slightly higher risk of developing HT (Pérez Fontán *et al*, 1999). Conversely, in a retrospective study which included 567 participants, male gender was independently associated with HT in KTR (Yu *et al*, 2016).

Allograft outcomes may have been influenced by several factors related to donor obesity as well. First, obese people are prone to a condition known as "obesity-related glomerulopathy" (Table 1.2). Second, a few studies have shown that donor obesity is associated with increased risk for delayed graft function (DGF) and graft failure (Naik *et al*, 2020). These in turn can lead to HT. However, in a national cohort study with 66382 deceased donors, the authors found that if the kidneys were of good quality (Kidney Donor Profile Index ≤30%), obesity was not associated with a lower graft survival compared to non-obese donors (Homkrailas *et al*, 2021).

It is important to note that there is a debate about whether BMI is the most accurate indicator of obesity. Other anthropometric measurements, like body surface area (BSA), waist circumference, and waits-hip ratio, are widely utilized in clinical contexts as well, but their results vary from one another.

Table 1.2: Proposed diagnostic criteria for obesity-related glomerulopathy (Wei *et al*, 2021)

BMI ≥30 (excluding endocrine obesity, drug-induced obesity and DM)
Isolated proteinuria without gross hematuria and obvious microscopic hematuria
Renal pathology manifestation of glomerular hypertrophy with or without FSGS[1,2]
Excluding obese patients with primary renal diseases, such as MN, IgA nephropathy and diabetic nephropathy

BMI, body mass index; DM, diabetes mellitus; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy

[1]Immunofluorescence may show nonspecific trapping of IgM and complement C3

[2]Obesity-realted glomerulopathy is usually associated with mild foot process effacement compared to primary FSGS

1.5.1.3   Donor Hypertension

Candidate eligibility for organ donation has traditionally been limited to healthy candidates without chronic diseases like HT and with a very low baseline risk of developing renal or cardiovascular disease. There is a risk of subclinical kidney disease being transmitted from donors with history of HT to the recipients, and, consequently, they may experience adverse outcomes. The effects of receiving a kidney transplant from a hypertensive donor on the recipient have only been the subject of a small number of research.

As an example, Yu *et al*. (2016) reported that donor HT emerged as one of the most significant risk factor for post-transplant HT (Odds ratio: 3.23; 95% CI: 1.05-9.96). Similarly, in a national cohort study from the United States with 71120 study participants, a greater risk of unfavorable outcomes was shown among allograft recipients from younger donors (age<50 years) who have HT (Al Ammary *et al*, 2021). However, a single-center retrospective study showed that at the time of transplantation and 1 year after transplantation, the diastolic and systolic BPs of recipients of normotensive and hypertensive donors were not significantly different (Dienemann *et al*, 2019). This study also failed to find a significant association between donor HT and recipient renal function after 3 years of follow-up.

Therefore, further studies with larger study participants are needed to illustrate if any correlation exist between donor HT and recipient HT.

1.5.1.4   Genetics

The possibility that a donor's genetic makeup plays a role in the pathophysiology of post-transplant HT is being supported by several research. As an example, the nephrotoxicity of CsA can occur in kidney grafts that were derived from donors carrying certain polymorphisms in ABCB1 or CYP3A5 (Hauser *et al*, 2005; Joy *et al*, 2007). Moreover, it has been found that certain KTR with the ABCC2 genotype have DGF (Grisk *et al*, 2009). There is also evidence that APOL-1 genotype has been associated with glomerulosclerosis and can adversely affect allograft function (Lee *et al*, 2012). HT after KTx has been connected to all of these clinical consequences, either directly or indirectly.

1.5.2 Recipient-related factors

1.5.2.1 Age, gender and BMI

Numerous studies have shown that age and gender of recipients are important factors in the development of HT following KTx. For instance, post-transplant HT is independently associated with male gender (Campistol *et al*, 2004; Yu *et al*, 2016). Another long-term risk factor for kidney graft loss is obesity among KTR at the time of transplantation, particularly among patients receiving deceased donor transplants after having long periods of dialysis (Yemini *et al*, 2022). It is therefore important to consider anthropometric measures, such as BMI, when assessing the potential recipients.

1.5.2.2 Immunosuppressive drugs

KTx has been replete with several groups of immunosuppressive agents. The most widely used medications are:

1. Corticosteroids (e.g., Prednisone)

2. Calcineurin inhibitors:

> ➢ Tacrolimus (FK-506, Prograf, Advagraf)
>
> ➢ Cyclosporine A (Neoral, Sandimmune)

3. Lymphocyte-selective purine synthesis inhibitors:

> ➢ Mycophenolate mofetil (MMF) (Cellcept)
>
> ➢ Mycophenolic acid (MPA) (Myfortic)

4. Mammalian target of rapamycin inhibitors (mTORi):

> ➢ Sirolimus (Rapamune)
>
> ➢ Everolimus (Certican, Novartis)

Among the aforementioned drugs, mycophenolate derivatives and mTORi are not associated with post-transplant HT. In contrast, the development of HT in KTR is significantly influenced by CNI and corticosteroids. Moreover, the effects of CsA on inducing and worsening HT are greater than those of Tac (Vincenti *et al*, 2002; Margreiter, 2002; Kramer *et al*, 2003). Figure 1.3 shows proposed mechanisms for CNI-induced HT.

There are multiple mechanisms by which corticosteroids may lead to HT; this include increase renal sodium reabsorption, upregulation in angiotensin II type I (AT-I) receptors and alterations in neuronal NO release (Goodwin and Geller, 2012).
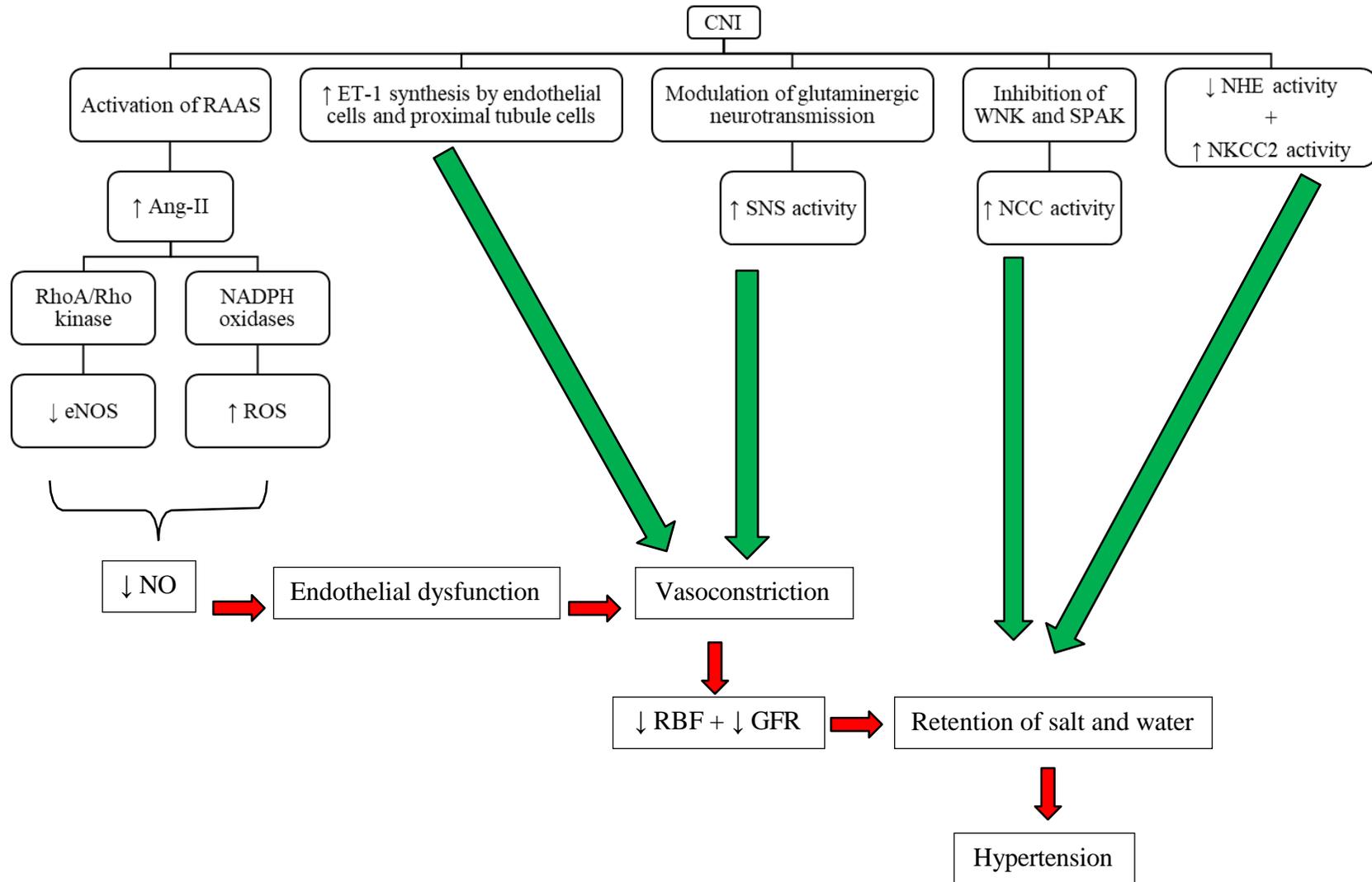
Figure 1-3. Pathogenesis of vasoconstriction and hypertension induced by CNIs (Hoskova *et al*, 2016; Calo *et al*, 2017).

It is likely that CNIs change the activities of all NOS isoforms through a variety of ways, resulting in a decrease in NO generation. In addition, it has been demonstrated that CNIs increase sodium reabsorption by increasing the activity of NCC and NKCC2. This is possible by preventing the inhibition of calcineurin's inhibitory effect on WNK, glucocorticoid-regulated kinase 1, SPAK (STE20/SPS1), and oxidative stress-responsive protein type 1 kinase NCC. Furthermore, By modulating glutaminergic neurotransmission, CsA stimulates sympathetic nervous activity which in turn can lead to vasoconstriction and HT.

RAAS, renin-angiotensin-aldosterone system; Ang-II, angiotensin-II; NADPH, nicotinamide adenine dinucleotide phosphate; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; NO, nitric oxide; ET-1, endothelin-1; SNS, sympathetic nervous system; WNK, with-no-lysine kinases; SPAK, STE20/SPS1-related proline alanine-rich kinases; NCC, sodium chloride cotransporter, NHE, Na^+-H^+ exchanger; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; RBF, renal blood flow; GFR, glomerular filtration rate.

1.5.2.3   Graft-related (chronic allograft injury/chronic allograft dysfunction)

According to a Spanish consensus report, CAI is defined as "a multifactorial clinical/pathological entity characterized by a progressive decrease in glomerular filtration rate (GFR), generally associated with proteinuria and arterial HT. Histologically, it manifests as interstitial fibrosis and tubular atrophy, although other types of non-specific lesions can also be observed" (Pascual *et al*, 2012). CAI has been associated with HT in several studies, but cause and effect cannot be determined. Therefore, identifying the precise role of CAI in development of HT has been challenging. Immunological and non-immunological causes have traditionally been attributed to CAI. Immunological factors include HLA-mismatching and acute rejection episodes. Major non-immunological factors leading to the development of CAI are HT, renal parenchymal disease (recurrent or de novo), dyslipidemia, infections (Epstein Barr virus, cytomegalovirus and BK virus), CNI toxicity and compliance of patients (Yilmaz, 2014).

1.5.2.4   Genetics

Patients who are CYP3A5*1 expressers and remain on corticosteroid therapy after receiving high Tac doses are at risk for developing CNI-related nephrotoxicity. This can further lead to chronic graft dysfunction and HT (Kuypers *et al*, 2010).

1.5.2.5   Biochemical factors (uric acid and parathyroid hormone)

Independent of the diagnosis of primary hyperparathyroidism, population-based studies report an association between increased parathyroid hormone levels and HT (Snijder *et al,* 2007; Taylor *et al*, 2008; Yao *et al*, 2016;). In a meta-analysis of six prospective cohort studies, a positive correlation between PTH and HT was observed (Relative risk: 1.35, 95% CI: .09 to 1.67) (Zhang Y and Zhang D-Z, 2018). Elevation of BP by PTH may occur as a result of increased renin release due to activation of the renin-angiotensin-aldosterone system (RAAS), impaired endothelial function, arterial stiffness, activation of the SNS and peripheral vasoconstriction (Pepe *et al*, 2017).

Since the parathyroid glands can become enlarged during late-stage chronic kidney disease (CKD) and dialysis and thus cause an increase in parathyroid hormone levels, KTR are exposed to a further risk of cardiovascular outcomes such as HT.

In a number of investigations, a link between hyperuricemia and HT has been suggested (Kuwabara *et al*, 2018; Yu *et al*, 2021).

Furthermore, it is believed that uric acid (UA) causes HT more prominently in young people and women (Grayson *et al*, 2011). Figure 1.4 shows the proposed mechanisms by which hyperuricemia lead to HT.

It is common for KTR to experience hyperuricemia. Hyperuricemia may develop for a variety of reasons, such as poor graft function (low GFR), immunosuppression (especially CsA) and diuretics (Clive, 2000). Kanbay *et al*. (2005) showed that both CsA and Tac are associated with elevated serum UA levels in KTR. However, the underlying mechanism by which these drugs can cause hyperuricemia is not clearly known.
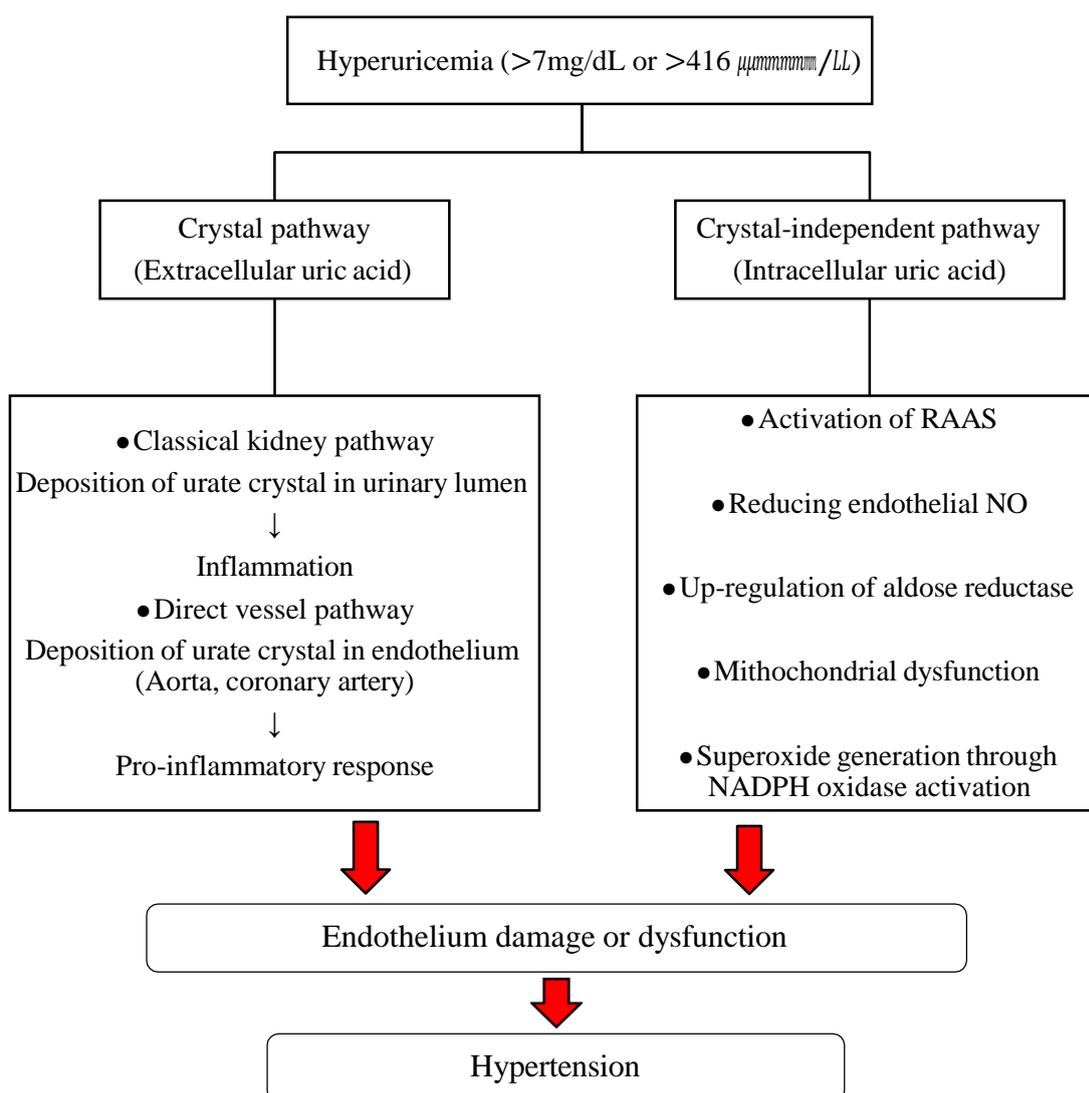
Figure 1-4. Proposed mechanisms by which hyperuricemia causes hypertension.

RAAS, renin-angiotensin-aldosterone system; NO, nitric oxide; NADPH, nicotinamide adenine dinucleotide phosphate (Lanaspa *et al*, 2020).

1.5.2.6 Surgical complications

1.5.2.6.1 Transplant renal artery stenosis (TRAS)

After KTx, TRAS typically becomes apparent between three months and two years, but it can appear at any time. In most cases, patients experience worsening or refractory HT, fluid retention, and/or allograft dysfunction without rejection evidence. HT caused by renal artery stenosis is due to activation of the RAAS and subsequently fluid and sodium retention (Bruno *et al*, 2004).

1.5.2.6.2 Page kidney (Page phenomenon)

A subcapsular or extrarenal collection of fluid causing renal hypoperfusion and ischemia, which results in activation of RAAS and elevation of BP, is known as Page kidney or Page phenomenon (Dopson *et al*, 2009). The clinical presentation of Page kidney varies significantly among the KTRs but it is generally associated with acute HT and a decline in renal function. Thus, Page kidney is an important risk factor for HT and close monitoring of BP following KTx is required.

1.5.2.6.3 Lymphocele

Patients who have received kidney transplants may also experience lymphatic problems. One of the lymphatic complications after KTx is known as lymphocele and it may take 2 weeks to 6 months after transplantation for it to develop (Ranghino *et al*, 2015). Lymphocele is defined as "fluid collection of any size near to the transplanted kidney, after urinoma, hematoma and abscess have been excluded" (Mehrabi *et al*, 2020). It has been discovered that there are numerous surgical and non-surgical predictors for the emergence of a symptomatic lymphocele (Jossten *et al*, 2019). In renal allograft recipients, lymphocele may compress the renal parenchyma, causing HT. In this case, the RAAS may be activated due to intrarenal ischemia. In conclusion, lymphatic complications in KTRs should be monitored closely.

1.6 Effects of high blood pressure on graft function

It has been shown that HT adversely affects kidney graft function and histology in laboratory studies. An experimental study in rats revealed that proteinuria increased progressively in hypertensive rats. Moreover, several cytokines and growth factors such as tumor necrosis factor alpha (TNF-α), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β) and interleukin-6 (IL-6) were also up-regulated in hypertensive rats compared to normotensive ones (Kusaka *et al*, 2002).

One of the most rigorous studies on the relationship between post-transplant BP and renal allograft outcomes in humans is the large multicenter Collaborative Transplant Study (CTS). This study which included 29,751 KTRs showed that at any DBP level, higher SBP was linked to lower graft survival (Opelz *et al*, 1998). There have been similar findings in other studies as well (Mange *et al*, 2000).

Therefore, the accumulation of all available data suggests that achieving optimal BP control can be a crucial therapeutic tool for improving the health of the patient and the outcome of the graft.

2   Aims of the study

> ➢ To determine the prevalence of post-transplant HT at 6 and 12 months in KTR
>
> ➢ To investigate the possible risk factors for HT at 6 and 12 months after KTx
>
> ➢ To evaluate the effect of HT on the function of the allograft at 6 and 12 months after KTx

3   Patients and methods

3.1   Study design and population

A retrospective cohort study was conducted at our KTx unit between January 1, 2007, and August 19, 2022. Data were collected from electronic medical records. The ethical committee of the Albert Szent-Györgyi Medical School approved this study (approval no. 27/2022).

3.2   Inclusion and exclusion criteria

438 patients were evaluated for inclusion (Figure 3-1). 158 subjects were excluded due to the following reasons:

(1) age <18 years;

(2) participants whose BP profiles were invalid or not available;

(3) recipients with less than 6-month follow-up;

(4) patients who lost to follow-up;

(5) recipients who died or returned to dialysis during follow-up and

(6) recipients using CsA as their main immunosuppressive regimen

Finally, 280 people were enrolled and stratified based on their BP profiles.

3.3   Definition and measurement of blood pressure

During outpatient visits, patients received education and standard training on measuring their BP at home according to the ESH/ESC guidelines.

Arterial HT was defined in accordance with ESH/ESC guidelines when SBP was $\geq$135 mmHg and/or DBP $\geq$85 mmHg. Based on the BP profile, two groups were considered: (1) normotensive/controlled group, patients without HT (SBP<135 and/or DBP<85) or HT controlled in the case of anti-hypertensive treatment; (2) hypertensive group, which included patients with SBP$\geq$135 and/or DBP$\geq$85.

3.4 Covariates

3.4.1 Recipients-related

Variables in our study included age at the time of KTx, sex, BMI, cause of the end-stage renal disease (ESRD), history of HT, and prior KTx. This study also included total cholesterol, triglyceride, LDL and HDL cholesterol, UA level, creatinine, estimated glomerular filtration rate (eGFR), and urine protein-creatinine ratio (UPCR).

eGFR was calculated using the Chronic kidney Disease Epidemiology Collaboration equation (CKD-EPI 2021) according to the following table:

Sex	Serum creatinine (mg/dL)	Equation
Female	≤0.7	$142 \times (Scr/0.7)^{-0.241} \times 0.9938^{Age} \times 1.012$
Female	>0.7	$142 \times (Scr/0.7)^{-1.200} \times 0.9938^{Age} \times 1.012$
Male	≤0.9	$142 \times (Scr/0.9)^{-0.302} \times 0.9938^{Age}$
Male	>0.9	$142 \times (Scr/0.9)^{-1.200} \times 0.9938^{Age}$

3.4.2 Donor-related

Age, sex, history of HT, and type of donor (deceased vs living) were included.

3.4.3 Transplant-related

Cold ischemia time (CIT), HLA mismatches, and immunosuppressive drugs (steroid use and Tac level) were included.

Patients transplanted between January 1, 2007 and August 19, 2022 (n=438)

Exclusion criteria:
►Less than 6 months follow up (n=6)
►Age <18 years (n=2)
►Loss to follow up (n=2)
►Returned to dialysis/Died during follow up (n=65)
►Missing/invalid data on BP (n=68)
►Cyclosporine use (n=15)

Analyzed in this study (n=280)

Complete analysis (n=189)

After multiple imputation (n=280)

6 month

Normotensive/Controlled HTN (n=94)

Hypertensive group (n=95)

Normotensive/Controlled HTN (n=142)

Hypertensive group (n=138)

12 month

Normotensive/Controlled HTN (n=76)

Hypertensive group (n=107)

Normotensive/Controlled HTN (n=126)

Hypertensive group (n=145)

Figure 3-1. Flowchart of the study

3.5   Statistical analysis

The normality of the data was checked using the Kolmogorov-Smirnov test, Q-Q plot, skewness, and kurtosis. If data were normally distributed, we reported means and standard deviations, and in the case of non-normally distributed data, medians and interquartile ranges. The categorical variables were described with numbers (percentages) and were analyzed by the Chi-square test or Fisher's exact test. Differences in continuous variables between groups were compared using the Student t-test or Mann-Whitney U-test as appropriate.

Logistic regression was used to estimate both the unadjusted and adjusted odds ratio (OR) to identify the potential risk factors for post-transplant HT. The multivariable model included predictors having clinically meaningful associations with HT and those with significant P-values in the univariable analysis. Variance inflation factor (VIF) was used to check the degree of multicollinearity. VIF > 10 was considered indicative of multicollinearity.

HT status of donors was unknown in 32% of cases (missing completely at random). Therefore, using the multiple imputation approach, 32 imputations were performed to account for missing data. Multiple imputed results were compared with the complete case analysis (before multiple imputation).

Statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS version 25.0; Armonk, NY: IBM Corporation) and RStudio version 4.1.3. The P-value of <0.05 was considered statistically significant.

4 Results

4.1 Before multiple imputation

4.1.1 At 6 months post-transplantation

4.1.1.1 *Characteristics and clinical features of recipients*

The demographic and characteristics of 189 kidney recipients are summarized in Table 4-1. Among them, 112 (59.3%) were male and 77 (40.7%) were female. The prevalence of HT at 6 months post-transplantation was 50.2%.

The average age of patients at the time of transplantation was 48.6 ± 12.2 years and the median age of donors was 53 years (42.0-61.0). 38 recipients (20.1%) had prior KTx and the majority of patients received allografts from deceased donors (89.9%). The most frequent cause of ESRD was glomerulonephritis (35.4%), followed by polycystic kidney disease (18.5%), HT (13.2%), and diabetes (3.2%).

There were significant differences in recipient gender ($P = 0.023$) and HT status of donors ($P = 0.011$) between the hypertensive and normotensive/controlled groups. Moreover, mean CIT was greater for those who developed arterial HT (10.1 ±5.6 vs 11.8 ±5.5 hrs; $P = 0.042$).

4.1.1.2 *Laboratory findings*

The biochemical profile of the patients at 6 months post-transplantation is presented in Table 4-2. The mean eGFR was 49.9 ±17.5 mL/min/1.73. The median total cholesterol level was higher in the hypertensive group than in the normotensive/controlled group (5.1 [4.2-6.0] vs 5.4 [4.9-6.2] mmol/L; $P = 0.037$). In addition, the serum UA level was higher in the hypertensive group than in the normotensive/controlled group (352 [297-396] vs 379 [335-449] μmol/L; $P = 0.009$).

No differences in Tac level, creatinine, eGFR, triglyceride, HDL, LDL, and UPCR were observed between either group.

Table 4-1. Recipient and donor baseline characteristics at 6 months post-transplantation (before multiple imputation)

	Overall (n = 189)	Normotensive/Controlled HT (n = 94)	Hypertensive (n = 95)	*P*-value
Recipient data				
Age at the time of KTx (years), mean (SD)	48.6 (12.2)	47.7 (12.5)	49.5 (12.0)	0.309
Gender				**0.023**
Male, n (%)	112 (59.3)	48 (51.1)	64 (67.4)	
Female, n (%)	77 (40.7)	46 (48.9)	31 (32.6)	
BMI (Kg/m^2), median (IQR)	25.9 (22.8-29.5)	24.9 (22.4-29.6)	26.7 (23.4-29.3)	0.165
BMI categories, n (%)				0.074
<18.5	2 (1.1)	1 (1.1)	1 (1.1)	
18.5-24.9	78 (41.3)	46 (48.9)	32 (33.7)	
25-29.9	65 (34.4)	25 (26.6)	40 (42.1)	
≥30	44 (23.3)	22 (23.4)	22 (23.2)	
Cause of ESRD, n (%)				0.397
Glomerulonephritis	67 (35.4)	34 (36.2)	33 (34.9)	
Polycystic kidney disease	35 (18.5)	20 (21.3)	15 (15.8)	
Hypertension	25 (13.2)	8 (8.5)	17 (17.9)	
Diabetes	6 (3.2)	3 (3.2)	3 (3.2)	
Others	56 (29.6)	29 (30.9)	27 (28.4)	
History of hypertension, n (%)				0.050
Yes	164 (86.8)	77 (81.9)	87 (91.6)	
No	25 (13.2)	17 (18.1)	8 (8.4)	
Prior KTx, n (%)				0.157
Yes	38 (20.1)	15 (16.0)	23 (24.2)	
No	151 (79.9)	79 (84.0)	72 (75.8)	

Cont.

Steroid use, n (%)				
Yes	177 (93.7)	87 (92.6)	90 (94.7)	0.538
No	12 (6.3)	7 (7.4)	5 (5.3)	
Cold ischemia time (hrs), mean (SD)	11.0 (5.6)	10.1 (5.6)	11.8 (5.5)	**0.042**
Cold ischemia time distribution, n (%)				
<12hr	98 (51.9)	55 (58.5)	43 (45.3)	
12-18hr	66 (34.9)	31 (33.0)	35 (36.8)	0.052
18-24hr	24 (12.7)	7 (7.4)	17 (17.9)	
>24hr	1 (0.5)	1 (1.1)	0	
Number of HLA mismatches, n (%)				
0-3	132 (69.8)	66 (70.2)	66 (69.5)	0.912
4-6	57 (30.2)	28 (29.8)	29 (39.5)	
Donor data				
Age, median (IQR)	53 (42-61)	53 (42-59)	53 (43.5-63)	0.193
Gender, n (%)				
Male	108 (57.1)	58 (61.7)	50 (52.6)	0.208
Female	81 (42.9)	36 (38.3)	45 (47.4)	
History of HT, n (%)				
Yes	102 (54.0)	42 (44.7)	60 (63.2)	**0.011**
No	87 (46.0)	52 (55.3)	35 (36.8)	
Type of donor, n (%)				
Deceased	170 (89.9)	81 (86.2)	89 (93.7)	0.086
Living	19 (10.1)	13 (13.8)	6 (6.3)	

KTx: kidney transplantation, BMI: body mass index, ESRD: end stage renal disease,

Table 4-2. Laboratory findings at 6 months post-transplantation (before multiple imputation)

	Overall (n = 189)	Normotensive/Controlled HT (n = 94)	Hypertensive (n = 95)	*P*-value
SBP, median (IQR) (mmHg)	130 (120-140)	121 (120-130)	140 (135-145)	**<0.001**
DBP, median (IQR) (mmHg)	80 (78-85)	80 (75-80)	85 (80-90)	**<0.001**
Tac level, median (IQR) (ng/ml)	8.6 (6.8-10.6)	8.6 (6.8-10.5)	8.5 (6.9-10.6)	0.884
Creatinine, median (IQR), (μmol/L)	136 (111-171)	130 (108-170)	145 (116-171.5)	0.188
eGFR, mean (SD) (mL/min/1.73m^2)	49.9 (17.5)	50.6 (17.5)	49.1 (17.5)	0.573
Total cholesterol, median (IQR) (mmol/L)	5.3 (4.6-6.1)	5.1 (4.2-6.0)	5.4 (4.9-6.2)	**0.037**
Triglyceride, median (IQR) (mmol/L)	2.0 (1.4-2.9)	2.0 (1.4-2.7)	2.1 (1.5-3.1)	0.238
HDL, median (IQR) (mmol/L)	1.3 (1.1-1.6)	1.2 (1.0-1.6)	1.3 (1.1-1.5)	0.336
LDL, median (IQR) (mmol/L)	2.8 (2.3-3.6)	2.7 (2.1-3.5)	3.1 (2.4-3.6)	0.136
Serum uric acid, median (IQR) (μmol/L)	362 (314-434.5)	352 (297-396)	379 (335-449)	**0.009**
UPCR, median (IQR) (mg/mmol)	15.4 (11.6-26.5)	14.6 (11.0-22.8)	16.2 (11.8-30.0)	0.107

SBP: systolic blood pressure, DBP: diastolic blood pressure, Tac: tacrolimus, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, UPCR: urine protein-creatinine ratio

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4.1.2 At 12 months post-transplantation

4.1.2.1 *Characteristics and clinical features of recipients*

Of 183 recipients who remained in the study, 109 (59.6%) were male and 74 (40.4%) were female (Table 4-3). The prevalence of HT at 12 months post-transplantation was 58.4%.

Recipients with arterial HT were older (50.1 ±11.7 vs 46.3 ±12.4 years; $P = 0.037$) and showed significantly higher BMI than the normotensive/controlled group (26.2 [23.4-30.5] vs 24.6 [22.5-28.7] Kg/m^2; $P = 0.028$). The median age of donors was higher in the hypertensive group than the normotensive/controlled group (56 [44.5-62.5] vs 50 [42-59] years; $P = 0.025$). Furthermore, the mean CIT of the hypertensive group was greater than the normotensive/controlled group (11.7 ±5.7 vs 10.0 ±5.1 hrs; $P = 0.049$). There were no significant statistical differences in the cause of ESRD, previous history of HT, number of HLA mismatches, gender of donor, and type of donor between two groups.

4.1.2.2 *Laboratory findings*

The biochemical profile of the patients at 12 months post-transplantation is presented in Table 4-4. In the laboratory findings, no difference was found between the two groups with respect to lipid parameters, creatinine, eGFR, UPCR, Tac level, and serum UA.

4.1.3 Risk factors of post-transplant HT at 6 and 12 months

Tables 4-5, 4-6 and 4-7 present the results of the univariate and multivariable analyses. After adjusting for confounders (model 4), the following factors were significantly linked to the development of arterial HT at 6 months: male gender (AOR: 2.192, 95% CI: 1.099-4.375; $P = 0.026$), hypertensive donor (AOR: 2.258, 95% CI:1.131-4.506; $P = 0.021$) and serum UA level (AOR: 1.004, 95% CI: 1.000-1.008; $P = 0.031$). However, only the male gender (AOR: 2.692, 95% CI: 1.275-5.684; $P = 0.009$) and serum UA level (AOR: 1.005, 95% CI: 1.000-1.010; $P = 0.039$) were independent risk factors at 12 months post-transplantation.

Table 4-3. Recipient and donor baseline characteristics at 12 months post-transplantation (before multiple imputation)

	Overall (n = 183)	Normotensive/Controlled HT (n = 76)	Hypertensive (n = 107)	*P*-value
Recipient data				
Age at the time of KTx (years), mean (SD)	48.5 (12.1)	46.3 (12.4)	50.1 (11.7)	**0.037**
Gender				
Male, n (%)	109 (59.6)	37 (48.7)	72 (67.3)	**0.011**
Female, n (%)	74 (40.4)	39 (51.3)	35 (32.7)	
BMI (Kg/m², median (IQR)	25.9 (22.8-29.6)	24.6 (22.5-28.7)	26.2 (23.4-30.5)	**0.028**
BMI categories, n (%)				
<18.5	2 (1.1)	2 (2.6)	0	0.057
18.5-24.9	75 (41.0)	37 (48.7)	38 (35.5)	
25-29.9	63 (34.4)	24 (31.6)	39 (36.4)	
≥30	43 (23.5)	13 (17.1)	30 (28.0)	
Cause of ESRD, n (%)				
Glomerulonephritis	64 (35.0)	28 (36.8)	36 (33.6)	0.352
Polycystic kidney disease	34 (18.6)	14 (18.4)	20 (18.7)	
Hypertension	25 (13.7)	6 (7.9)	19 (17.8)	
Diabetes	6 (3.3)	2 (2.6)	4 (3.7)	
Others	54 (29.5)	26 (34.2)	28 (26.2)	
History of hypertension, n (%)				
Yes	159 (86.9)	66 (86.8)	93 (86.9)	0.988
No	24 (13.1)	10 (13.2)	14 (13.1)	
Prior KTx, n (%)				
Yes	35 (19.1)	21 (27.6)	14 (13.1)	**0.014**
No	148 (80.9)	55 (72.4)	93 (86.9)	

Cont.

Steroid use, n (%)				
Yes	155 (84.7)	61 (80.3)	94 (87.9)	0.160
No	28 (15.3)	15 (19.7)	13 (12.1)	
Cold ischemia time (hrs), mean (SD)	11.0 (5.5)	10.0 (5.1)	11.7 (5.7)	**0.049**
Cold ischemia time distribution, n (%)				
<12hr	95 (51.9)	44 (57.9)	51 (47.7)	
12-18hr	64 (35.0)	28 (36.8)	36 (33.6)	**0.040**
18-24hr	23 (12.6)	4 (5.3)	19 (17.8)	
>24hr	1 (0.5)	0	1 (0.9)	
Number of HLA mismatches, n (%)				
0-3	127 (69.4)	53 (69.7)	74 (69.2)	0.933
4-6	56 (30.6)	23 (30.3)	33 (30.8)	
Donor data				
Age, median (IQR)	53 (43-61)	50 (42-59)	56 (44.5-62.5)	**0.025**
Gender, n (%)				
Male	105 (57.4)	46 (60.5)	59 (55.1)	0.468
Female	78 (42.6)	30 (39.5)	48 (44.9)	
History of HT, n (%)				
Yes	100 (54.6)	36 (47.4)	64 (59.8)	0.096
No	83 (45.4)	40 (52.6)	43 (40.2)	
Type of donor, n (%)				
Deceased	166 (90.7)	66 (86.8)	100 (93.5)	0.129
Living	17 (9.3)	10 (13.2)	7 (6.5)	

KTx: kidney transplantation, BMI: body mass index, ESRD: end stage renal disease,

Table 4-4. Laboratory findings at 12 months post-transplantation (before multiple imputation)

	Overall (n = 183)	Normotensive/Controlled HTN (n = 76)	Hypertensive (n = 107)	*P*-value
SBP, median (IQR) (mmHg)	132 (129-140)	126.5 (120-130)	140 (135-140)	**<0.001**
DBP, median (IQR) (mmHg)	80 (77-85)	80 (75-80)	84 (78-90)	**<0.001**
Tac level, median (IQR) (ng/mL)	7.7 (6.3-9.2)	8.0 (6.6-9.0)	7.5 (6.0-9.2)	0.335
Creatinine, median (IQR), ($\mu\mu$mol/L)	127 (109-161)	127 (109.5-158)	127 (109-161)	0.555
eGFR, mean (SD) (mL/min/1.73m^2)	53.3 (16.6)	53.9 (17.5)	52.9 (16.1)	0.677
Total cholesterol, median (IQR) (mmol/L)	5.4 (4.6-6.2)	5.6 (4.6-6.2)	5.3 (4.6-6.1)	0.416
Triglyceride, median (IQR) (mmol/L)	1.8 (1.3-2.7)	1.6 (1.2-2.4)	1.9 (1.3-2.8)	0.130
HDL, median (IQR) (mmol/L)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.3 (1.1-1.5)	0.997
LDL, median (IQR) (mmol/L)	2.9 (2.4-3.6)	3.2 (2.5-3.7)	2.9 (2.3-3.5)	0.124
Serum uric acid, median (IQR) ($\mu\mu$mol/L)	352 (304-422)	338 (293.5-404.5)	359 (314.5-429.5)	0.058
UPCR, median (IQR) (mg/mmol)	13.7 (9.9-20.6)	13.1 (10.0-18.3)	14.1 (9.8-24.7)	0.319

SBP: systolic blood pressure, DBP: diastolic blood pressure, Tac: tacrolimus, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, UPCR: urine protein-creatinine ratio

Table 4-5. Univariate analysis of possible risk factors for hypertension after transplantation (before multiple imputation)

	At 6 month			At 12 month		
	Crude OR	95% CI	P-value	Crude OR	95% CI	*P*-value
Recipient factors						
Age of recipient at the time of KTx	1.012	0.989-1.036	0.307	1.027	1.001-1.052	**0.039**

Gender of recipient
    Female
    Male
	Ref
	1.978
		1.097-3.567	**0.023**	Ref
				2.168
					1.185-3.909	**0.012**

BMI at the time of KTx <25 ≥25	Ref 1.879	1.047-3.371	**0.035**	Ref 1.914	1.051-3.485	**0.034**

Prior KTx
    No
    Yes
	Ref
	1.682
		0.815-3.472	0.159	Ref
				0.394
					0.186-0.838	**0.016**

History of HT No Yes	Ref 2.401	0.982-5.873	0.055	Ref 1.006	0.421-2.404	0.988

Steroid use
    No
    Yes
	Ref
	1.448
		0.443-4.736	0.540	Ref
				1.778
					0.791-3.995	0.164

HLA mismatches
    0-3
    4-6
	Ref
	1.036
		0.556-1.928	0.912	Ref
				1.028
					0.543-1.946	0.933

Cont.

	At 6 month			At 12 month		
	Crude OR	**95% CI**	***P*-value**	**Crude OR**	**95% CI**	***P*-value**
Donor factors						
Age of donor						
<50	Ref	0.499-1.595	0.701	Ref	0.933-3.106	0.083
≥50	0.893			1.703		
Gender of donor						
Female	Ref	0.387-1.230	0.208	Ref	0.447-1.457	0.468
Male	0.690			0.802		
Hypertensive donor						
No	Ref	1.186-3.800	**0.011**	Ref	0.914-2.993	0.097
Yes	2.122			1.654		
Type of donor						
Living	Ref	0.864-6.556	0.093	Ref	0.785-5.971	0.136
Deceased	2.381			2.165		
Biochemical profile of the recipient						
LDL (1 mmol/L increase)	1.207	0.940-1.550	0.140	0.787	0.594-1.044	0.097
Triglyceride (1 mmol/L increase)	1.160	0.915-1.471	0.221	1.035	0.862-1.242	0.712
Uric acid (1 $\mu\mu$mol/L increase)	1.004	1.001-1.008	**0.007**	1.004	1.001-1.008	**0.020**
Cold ischemia time (1-h increase)	1.055	1.001-1.111	**0.044**	1.056	1.000-1.115	0.051
Tac level (1 ng/mL increase)	1.012	0.925-1.106	0.800	0.944	0.834-1.069	0.365

Table 4-6. Multivariable analysis of possible risk factors for hypertension at 6 months post-transplantation (before multiple imputation)

	Model 1 AOR (95%CI)	*P*-value	Model 2 AOR (95%CI)	*P*-value	Model 3 AOR (95%CI)	*P*-value	Model 4 AOR (95%CI)	*P*-value
Recipient and donor factors								
Age of recipient (1-year increase)	1.011 (0.986-1.037)	0.381	1.009 (0.981-1.038)	0.523	1.009 (0.980-1.039)	0.559	1.010 (0.981-1.041)	0.503
Gender of recipient								
Female	Ref	**0.018**	Ref	**0.019**	Ref	**0.031**	Ref	**0.026**
Male	2.083 (1.136-3.819)		2.142 (1.134-4.048)		2.125 (1.070-4.220)		2.192 (1.099-4.375)	
BMI at the time of KTx								
<25	Ref	0.063	Ref	**0.047**	Ref	0.169	Ref	0.227
≥25	1.784 (0.969-3.284)		1.962 (1.009-3.816)		1.653 (0.807-3.383)		1.565 (0.757-3.234)	
Prior KTx								
No			Ref	0.129	Ref	0.094	Ref	0.140
Yes			1.876 (0.833-4.226)		2.074 (0.884-4.864)		1.925 (0.807-4.593)	
History of HT								
No			Ref	0.170	Ref	0.170	Ref	0.162
Yes			1.986 (0.746-5.288)		2.010 (0.741-5.453)		2.046 (0.750-5.583)	
Steroid use								
No				0.558		0.715		0.800
Yes			1.483 (0.424-5.189)		1.274 (0.346-4.688)		1.180 (0.315-4.419)	

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Cont.

	Model 1 AOR (95%CI)	*P*-value	Model 2 AOR (95%CI)	*P*-value	Model 3 AOR (95%CI)	*P*-value	Model 4 AOR (95%CI)	*P*-value
Age of donor								
<50			Ref	0.152	Ref	0.197	Ref	0.180
≥50			0.601 (0.299-1.206)		0.621 (0.302-1.280)		0.610 (0.295-1.257)	
Gender of donor								
Female			Ref	0.241	Ref	0.186	Ref	0.234
Male			0.687 (0.367-1.286)		0.637 (0.326-1.243)		0.664 (0.338-1.304)	
Hypertensive donor								
No			Ref	**0.009**	Ref	**0.020**	Ref	**0.021**
Yes			2.411 (1.251-4.648)		2.265 (1.136-4.516)		2.258 (1.131-4.506)	
Type of donor								
Living					Ref	0.251	Ref	0.678
Deceased					1.980 (0.616-6.358)		1.354 (0.324-5.663)	
LDL (1 mmol/L increase)					1.221 (0.926-1.609)	0.157	1.217 (0.919-1.612)	0.171
Triglyceride (1 mmol/L increase)					1.044 (0.792-1.377)	0.758	1.046 (0.791-1.384)	0.750
Uric acid (1 $\mu\mu$mol/L increase)					1.004 (1.000-1.007)	**0.037**	1.004 (1.000-1.008)	**0.031**
Cold ischemia time (1-h increase)							1.036 (0.961-1.115)	0.357
Tac level (1 ng/mL increase)							0.987 (0.892-1.092)	0.800

Table 4-7. Multivariable analysis of possible risk factors for hypertension at 12 months post-transplantation (before multiple imputation)

	Model 1 AOR (95%CI)	P-value	Model 2 AOR (95%CI)	P-value	Model 3 AOR (95%CI)	P-value	Model 4 AOR (95%CI)	P-value
Recipient and donor factors								
Age of recipient (1-year increase)	1.029 (1.001-1.057)	**0.040**	1.021 (0.990-1.053)	0.188	1.026 (0.993-1.061)	0.129	1.024 (0.990-1.059)	0.167
Gender of recipient								
Female	Ref	**0.004**	Ref	**0.005**	Ref	**0.026**	Ref	**0.009**
Male	2.522 (1.334-4.70)		2.591 (1.336-5.026)		2.267 (1.102-4.665)		2.692 (1.275-5.684)	
BMI at the time of KTx								
<25	Ref	0.113	Ref	0.280	Ref	0.553	Ref	0.884
≥25	1.671 (0.885-3.156)		1.459 (0.735-2.896)		1.244 (0.605-2.556)		1.057 (0.501-2.233)	
Prior KTx								
No			Ref	**0.034**	Ref	**0.028**	Ref	**0.009**
Yes			0.405 (0.176-0.935)		0.370 (0.153-0.897)		0.282 (0.109-0.728)	
History of HT								
No			Ref	0.695	Ref	0.668	Ref	0.787
Yes			0.823 (0.311-2.181)		0.803 (0.294-2.194)		0.869 (0.313-2.409)	
Steroid use								
No				0.301		0.101		0.173
Yes			1.592 (0.660-3.839)		1.961 (0.765-5.024)		1.951 (0.738-5.160)	

Cont.

	Model 1 AOR (95%CI)	*P*-value	Model 2 AOR (95%CI)	*P*-value	Model 3 AOR (95%CI)	*P*-value	Model 4 AOR (95%CI)	*P*-value
Age of donor								
<50			Ref	0.299	Ref	0.262	Ref	0.323
≥50			1.460 (0.715-2.983)		1.540 (0.724-3.274)		1.475 (0.683-3.187)	
Gender of donor								
Female			Ref	0.265	Ref	0.191	Ref	0.196
Male			0.687 (0.355-1.329)		0.621 (0.304-1.268)		0.619 (0.299-1.281)	
Hypertensive donor								
No			Ref	0.252	Ref	0.454	Ref	0.411
Yes			1.476 (0.758-2.875)		1.309 (0.647-2.647)		1.352 (0.659-2.776)	
Type of donor								
Living					Ref	0.209	Ref	0.777
Deceased					2.266 (0.632-8.127)		1.248 (0.270-5.770)	
LDL (1 mmol/L increase)					0.738 (0.530-1.026)	0.070	0.715 (0.506-1.010)	0.057
Triglyceride (1 mmol/L increase)					1.001 (0.825-1.214)	0.994	0.999 (0.817-1.222)	0.992
Uric acid (1 μmol/L increase)					1.005 (1.000-1.009)	**0.035**	1.005 (1.000-1.010)	**0.039**
Cold ischemia time (1-h increase)							1.081 (0.996-1.173)	0.061
Tac level (1 ng/mL increase)							0.879 (0.757-1.021)	0.093

4.2   After multiple imputation

4.2.1   At 6 months post-transplantation

4.2.1.1   *Characteristics and clinical features of recipients*

The demographic and characteristics of 280 KTR are summarized in Table 4-8. Among them, 158 (56.4%) were male and 122 (43.6%) were female. The prevalence of HT at 6 months was 49.3%.

The mean age of patients at the time of transplantation was 48.3 ± 12.3 years and the median age of donors was 51 years (42.0-59.0). 55 recipients (19.6%) had prior KTx and the majority of patients received allografts from deceased donors (93.2%).

There were significant differences in recipient gender ($P = 0.028$) between the hypertensive and normotensive/controlled groups. However, no significant differences were found with regard to age at the time of KTx, BMI, cause of ESRD, history of HT, prior KTx, steroid use, CIT, number of HLA mismatches, and donor characteristics.

4.2.1.2   *Laboratory findings*

The biochemical profile of the patients at 6 months post-transplantation is presented in Table 4-9. The mean eGFR was 51.8 ± 18.2 mL/min/1.73. Lipid and renal parameters showed no significant differences between the hypertensive and normotensive/controlled groups.

Table 4-8. Recipient and donor baseline characteristics at 6 months post-transplantation (after multiple imputation)

	Overall (n = 280)	Normotensive/Controlled HT (n = 142)	Hypertensive (n = 138)	*P*-value
Recipient data				
Age at the time of KTx (years), mean (SD)	48.3 (12.3)	47.8 (12.5)	48.9 (12.1)	0.473
Gender				
Male, n (%)	158 (56.4)	71 (50.0)	87 (63.0)	**0.028**
Female, n (%)	122 (43.6)	71 (50.0)	51 (37.0)	
BMI (Kg/m^2), mean (SD)	26.0 (4.5)	25.6 (4.7)	26.4 (4.2)	0.156
BMI categories, n (%)				
<18.5	7 (2.5)	6 (4.2)	1 (0.7)	**0.030**
18.5-24.9	114 (40.7)	64 (45.1)	50 (36.2)	
25-29.9	105 (37.5)	43 (30.3)	62 (44.9)	
≥30	54 (19.3)	29 (20.4)	25 (18.1)	
Cause of ESRD, n (%)				
Glomerulonephritis	95 (33.9)	50 (35.2)	45 (32.6)	
Polycystic kidney disease	61 (21.8)	37 (26.1)	24 (17.4)	0.113
Hypertension	33 (11.8)	11 (7.7)	22 (15.9)	
Diabetes	11 (3.9)	4 (2.8)	7 (5.1)	
Others	80 (28.6)	40 (28.2)	40 (29.0)	
History of hypertension, n (%)				
Yes	236 (84.3)	115 (81.0)	121 (87.7)	0.124
No	44 (15.7)	27 (19.0)	17 (12.3)	
Prior KTx, n (%)				
Yes	55 (19.6)	25 (17.6)	30 (21.7)	0.384
No	225 (80.4)	117 (82.4)	108 (78.3)	

Cont.

Steroid use, n (%)				
Yes	263 (93.9)	131 (92.3)	132 (95.7)	0.234
No	17 (6.1)	11 (7.7)	6 (4.3)	
Cold ischemia time (hrs), median (IQR)	13.1 (8.4-16.3)	12.3 (8.4-15.4)	13.3 (9.0-17.0)	0.221
Cold ischemia time distribution, n (%)				
<12hr	116 (41.4)	66 (46.5)	50 (36.2)	
12-18hr	115 (41.1)	55 (38.7)	60 (43.5)	0.099
18-24hr	47 (16.8)	19 (13.4)	28 (20.3)	
>24hr	2 (0.7)	2 (1.4)	0	
Number of HLA mismatches, n (%)				
0-3	203 (72.5)	103 (72.5)	100 (72.5)	0.989
4-6	77 (27.5)	39 (27.5)	38 (27.5)	
Donor data				
Age, median (IQR)	51 (42-59)	51 (41-58)	51.5 (43-60)	0.138
Gender, n (%)				
Male	165 (58.9)	90 (63.4)	75 (54.3)	0.125
Female	115 (41.1)	52 (36.6)	63 (45.7)	
History of HT, n (%)				
Yes	102 (36.4)	42 (29.6)	60 (43.5)	0.097[a]
No	87 (31.1)	52 (36.6)	35 (25.3)	
Unknown	91 (32.5)	48 (33.8)	43 (31.2)	
Type of donor, n (%)				
Deceased	261 (93.2)	129 (90.8)	132 (95.7)	0.110
Living	19 (6.8)	13 (9.2)	6 (4.3)	

[a] Pooled result; KTx: kidney transplantation, BMI: body mass index, ESRD: end stage renal disease,

Table 4-9. Laboratory findings at 6 months post-transplantation (after multiple imputation)

	Overall (n = 280)	Normotensive/Controlled HT (n = 142)	Hypertensive (n = 138)	*P*-value
SBP, median (IQR) (mmHg)	130 (120-140)	123 (120-130)	140 (135-145)	**<0.001**
DBP, median (IQR) (mmHg)	80 (76.2-85)	80 (74-80)	85 (80-90)	**<0.001**
Tac level, median (IQR) (ng/ml)	8.2 (6.4-10.4)	8.4 (6.4-10.4)	8.1 (6.4-10.4)	0.847
Creatinine, median (IQR), (μmol/L)	130 (108.2-168)	124 (103-167)	135 (114-168)	0.059
eGFR, mean (SD) (mL/min/1.73m^2)	51.8 (18.2)	52.9 (18.7)	50.6 (17.6)	0.279
Total cholesterol, median (IQR) (mmol/L)	5.2 (4.4-6.0)	5.2 (4.2-6.0)	5.2 (4.6-6.0)	0.285
Triglyceride, median (IQR) (mmol/L)	2.0 (1.3-2.8)	1.9 (1.4-2.7)	2.0 (1.3-3.0)	0.356
HDL, median (IQR) (mmol/L)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.3 (1.1-1.5)	0.738
LDL, median (IQR) (mmol/L)	2.8 (2.2-3.5)	2.7 (2.1-3.5)	2.8 (2.4-3.5)	0.667
Serum uric acid, median (IQR) (μmol/L)	357 (302.2-420.7)	352 (294-408)	364 (311-429)	0.120
UPCR, median (IQR) (mg/mmol)	14.9 (10.8-26.0)	14.6 (10.9-23.8)	15.5 (10.8-28.8)	0.207

SBP: systolic blood pressure, DBP: diastolic blood pressure, Tac: tacrolimus, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, UPCR: urine protein-creatinine ratio

4.2.2   At 12 months post-transplantation

4.2.2.1   *Characteristics and clinical features of recipients*

Of 271 recipients who remained in the study, 154 (56.8%) were male and 117 (43.2%) were female (Table 4-10). The prevalence of HT at 12 months was 53.5%. Hypertensive group was older and had longer CIT but these findings did not reach statistical significance.

Recipients with arterial HT showed significantly higher BMI than the normotensive/controlled group (26.8 ±4.3 vs 25.3 ±4.4 Kg/m^2; P = 0.006). The median age of donors was higher in the hypertensive group than the normotensive/controlled group (54 [44.0-61.0] vs 50 [41-57] years; P = 0.002). There were no significant differences in the cause of ESRD, previous history of HT, number of HLA mismatches, gender of donor, and type of donor between the two groups.

4.2.2.2   *Laboratory findings*

The biochemical profile of the patients at 12 months post-transplantation is presented in Table 4-11. The median creatinine level was higher in the hypertensive group than the normotensive/controlled group (126 [109-161] vs 119 [100-146] mmol/L; P = 0.038). In addition, the serum UA level was higher in the hypertensive group than the normotensive/controlled group (355 [314-428] vs 336.5 [297-400] μmol/L; P = 0.041). No significant differences were found with regard to lipid parameters, Tac level, and UPCR.

4.2.3   Risk factors of post-transplant HT at 6 and 12 months

Tables 4-12, 4-13 and 4-14 present the results of the univariate and multivariable analyses.

After multivariable adjustments (model 4), the predictive factors for arterial HT at 6 months were: male gender (AOR: 1.717, 95% CI: 1.007-2.927; P = 0.047) and hypertensive donor (AOR: 2.038, 95% CI:1.038-4.004; P = 0.039).

At 12 months post-transplantation the presence of HT was significantly associated with male gender (AOR: 2.048, 95% CI: 1.161-3.614; P = 0.013) and serum UA level (AOR: 1.004, 95% CI: 1.000-1.007; P = 0.033).

Table 4-10. Recipient and donor baseline characteristics at 12 months post-transplantation (after multiple imputation)

	Overall (n = 271)	Normotensive/Controlled HT (n = 126)	Hypertensive (n = 145)	*P*-value
Recipient data				
Age at the time of KTx (years), mean (SD)	49 (40-58)	46 (37-58)	51 (43-57)	0.062
Gender				**0.004**
Male, n (%)	154 (56.8)	60 (47.6)	94 (64.8)	
Female, n (%)	117 (43.2)	66 (52.4)	51 (35.2)	
BMI (Kg/m^2), mean (SD)	26.1 (4.4)	25.3 (4.4)	26.8 (4.3)	**0.006**
BMI categories, n (%)				**0.004**
<18.5	7 (2.6)	7 (5.6)	0	
18.5-24.9	108 (39.9)	55 (43.7)	53 (36.6)	
25-29.9	103 (38.0)	46 (36.5)	57 (39.3)	
≥30	53 (19.6)	18 (14.3)	35 (24.1)	
Cause of ESRD, n (%)				0.190
Glomerulonephritis	91 (33.6)	49 (38.9)	42 (29.0)	
Polycystic kidney disease	59 (21.8)	26 (20.6)	33 (22.8)	
Hypertension	33 (12.2)	10 (7.9)	23 (15.9)	
Diabetes	11 (4.1)	4 (3.2)	7 (4.8)	
Others	77 (28.4)	37 (29.4)	40 (27.6)	
History of hypertension, n (%)				0.405
Yes	229 (84.5)	104 (82.5)	125 (86.2)	
No	42 (15.5)	22 (17.5)	20 (13.8)	
Prior KTx, n (%)				0.050
Yes	51 (18.8)	30 (23.8)	21 (14.5)	
No	220 (81.2)	96 (76.2)	124 (85.5)	

Cont.

Steroid use, n (%)				
Yes	222 (81.9)	98 (77.8)	124 (85.5)	0.099
No	49 (18.1)	28 (22.2)	21 (14.5)	
Cold ischemia time (hrs), mean (SD)	12.3 (5.4)	11.9 (5.3)	12.6 (5.6)	0.308
Cold ischemia time distribution, n (%)				
<12hr	113 (41.7)	57 (45.2)	56 (38.6)	
12-18hr	112 (41.3)	54 (42.9)	58 (40.0)	0.145
18-24hr	44 (16.2)	14 (11.1)	30 (20.7)	
>24hr	2 (0.7)	1 (0.8)	1 (0.7)	
Number of HLA mismatches, n (%)				
0-3	195 (72.0)	94 (74.6)	101 (69.7)	0.366
4-6	76 (28.0)	32 (25.4)	44 (30.3)	
Donor data				
Age, median (IQR)	51 (42-59)	50 (41-57)	54 (44-61)	**0.002**
Gender, n (%)				
Male	162 (59.8)	77 (61.1)	85 (58.6)	0.677
Female	109 (40.2)	49 (38.9)	60 (41.4)	
History of HT, n (%)				
Yes	100 (36.9)	36 (28.6)	64 (44.1)	0.342[a]
No	83 (30.6)	40 (31.7)	43 (29.7)	
Unknown	88 (32.5)	50 (39.7)	38 (26.2)	
Type of donor, n (%)				
Deceased	254 (93.7)	116 (92.1)	138 (95.2)	0.292
Living	17 (6.3)	10 (7.9)	7 (4.8)	

[a] Pooled result; KTx: kidney transplantation, BMI: body mass index, ESRD: end stage renal disease,

Table 4-11. Laboratory findings at 12 months post-transplantation (after multiple imputation)

	Overall (n = 271)	Normotensive/Controlled HT (n = 126)	Hypertensive (n = 145)	*P*-value
SBP, median (IQR) (mmHg)	130 (126-140)	126 (120-130)	140 (135-143)	**<0.001**
DBP, median (IQR) (mmHg)	80 (77-85)	80 (75-80)	85 (80-90)	**<0.001**
Tac level, mean (SD) (ng/ml)	7.7 (2.4)	7.8 (2.4)	7.7 (2.4)	0.714
Creatinine, median (IQR), (μmol/L)	124 (106-156)	119 (100-146)	126 (109-161)	**0.038**
eGFR, mean (SD) (mL/min/1.73m^2)	55.1 (17.7)	56.9 (17.9)	53.5 (17.5)	0.111
Total cholesterol, median (IQR) (mmol/L)	5.2 (4.5-6.0)	5.3 (4.5-5.9)	5.2 (4.5-6.0)	0.723
Triglyceride, median (IQR) (mmol/L)	1.8 (1.3-2.7)	1.8 (1.2-2.4)	1.8 (1.3-2.8)	0.452
HDL, median (IQR) (mmol/L)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	1.3 (1.1-1.6)	0.590
LDL, mean (SD) (mmol/L)	2.9 (1.0)	3.0 (1.1)	2.8 (0.9)	0.290
Serum uric acid, median (IQR) (μmol/L)	344 (302-416)	336.5 (297-400)	355 (314-428)	**0.041**
UPCR, median (IQR) (mg/mmol)	13.9 (10.0-21.6)	13.7 (10.3-18.4)	14.0 (9.7-26.8)	0.394

SBP: systolic blood pressure, DBP: diastolic blood pressure, Tac: tacrolimus, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, UPCR: urine protein-creatinine ratio

Table 4-12. Univariate analysis of possible risk factors for hypertension post-transplantation (after multiple imputation)

	At 6 month			At 12 month		
	Crude OR	95% CI	*P*-value	Crude OR	95% CI	*P*-value
Recipient factors						
Age of recipient at the time of KTx	1.007	0.988-1.026	0.472	1.019	0.999-1.040	0.057

Gender of recipient
  Female
  Male
	Ref
	1.706
		1.059-2.749	**0.028**	Ref
				2.027
					1.244-3.304	**0.005**

BMI at the time of KTx <25 ≥25	Ref 1.658	1.029-2.673	**0.038**	Ref 1.682	1.034-2.734	**0.036**

Prior KTx
  No
  Yes
	Ref
	1.300
		0.719-2.349	0.385	Ref
				0.542
					0.292-1.005	0.052

History of HT No Yes	Ref 1.671	0.865-3.228	0.126	Ref 1.322	0.684-2.556	0.406

Steroid use
  No
  Yes
	Ref
	1.847
		0.664-5.142	0.240	Ref
				1.687
					0.903-3.151	0.101

HLA mismatches
  0-3
  4-6
	Ref
	1.004
		0.594-1.696	0.989	Ref
				1.280
					0.749-2.185	0.366

Cont.

	At 6 month			At 12 month		
	Crude OR	**95% CI**	***P*-value**	**Crude OR**	**95% CI**	***P*-value**
Donor factors						
Age of donor						
<50	Ref	0.628-1.613	0.978	Ref	0.949-2.497	0.080
≥50	1.007			1.540		
Gender of donor						
Female	Ref	0.426-1.110	0.125	Ref	0.554-1.468	0.677
Male	0.688			0.902		
Hypertensive donor	Ref					
No	1.942	1.083-3.481	**0.026**	Ref	0.891-2.730	0.119
Yes				1.560		
Type of donor						
Living	Ref	0.818-6.010	0.118	Ref	0.627-4.606	0.297
Deceased	2.217			1.700		
Biochemical profile of the recipient						
LDL (1 mmol/L increase)	1.056	0.860-1.297	0.604	0.882	0.698-1.114	0.291
Triglyceride (1 mmol/L increase)	1.161	0.951-1.417	0.142	0.993	0.851-1.158	0.926
Uric acid (1 μmol/L increase)	1.002	1.000-1.005	0.088	1.004	1.001-1.006	**0.011**
Cold ischemia time (1-h increase)	1.028	0.985-1.073	0.199	1.023	0.979-1.069	0.307
Tac level (1 ng/mL increase)	1.000	0.927-1.079	0.998	0.982	0.889-1.084	0.713

Table 4-13. Multivariable analysis of possible risk factors for hypertension at 6 months post-transplantation (after multiple imputation)

	Model 1 AOR (95%CI)	*P*-value	Model 2 AOR (95%CI)	*P*-value	Model 3 AOR (95%CI)	*P*-value	Model 4 AOR (95%CI)	*P*-value
Recipient and donor factors								
Age of recipient (1-year increase)	1.006 (0.985-1.026)	0.596	1.002 (0.980-1.024)	0.889	1.001 (0.978-1.024)	0.931	1.002 (0.979-1.025)	0.884
Gender of recipient								
Female	Ref	**0.028**	Ref	**0.042**	Ref	0.050	Ref	**0.047**
Male	1.729 (1.061-2.816)		1.693 (1.020-2.812)		1.700 (1.000-2.889)		1.717 (1.007-2.927)	
BMI at the time of KTx								
<25	Ref	0.071	Ref	0.058	Ref	0.163	Ref	0.169
≥25	1.584 (0.961-2.611)		1.670 (0.983-2.836)		1.481 (0.852-2.573)		1.482 (0.846-2.596)	
Prior KTx								
No			Ref	0.395	Ref	0.408	Ref	0.398
Yes			1.321 (0.695-2.512)		1.318 (0.685-2.535)		1.328 (0.688-2.564)	
History of HT								
No			Ref	0.155	Ref	0.166	Ref	0.157
Yes			1.677 (0.823-3.416)		1.654 (0.811-3.375)		1.678 (0.820-3.433)	
Steroid use								
No				0.219		0.249		0.251
Yes			1.958 (0.671-5.711)		1.899 (0.638-5.658)		1.901 (0.634-5.699)	

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Cont.

	Model 1 AOR (95%CI)	P-value	Model 2 AOR (95%CI)	P-value	Model 3 AOR (95%CI)	P-value	Model 4 AOR (95%CI)	P-value
Age of donor								
<50			Ref	0.309	Ref	0.316	Ref	0.323
≥50			0.749 (0.429-1.307)		0.750 (0.427-1.316)		0.752 (0.428-1.322)	
Gender of donor								
Female			Ref	0.102	Ref	0.066	Ref	0.064
Male			0.653 (0.391-1.088)		0.611 (0.361-1.034)		0.608 (0.358-1.030)	
Hypertensive donor								
No			Ref	**0.019**	Ref	**0.037**	Ref	**0.039**
Yes			2.176 (1.140-4.155)		2.047 (1.046-4.008)		2.038 (1.038-4.004)	
Type of donor								
Living					Ref	0.197	Ref	0.273
Deceased					2.071 (0.685-6.260)		2.061 (0.566-7.500)	
LDL (1 mmol/L increase)					1.064 (0.852-1.330)	0.583	1.062 (0.850-1.326)	0.597
Triglyceride (1 mmol/L increase)					1.086 (0.872-1.354)	0.461	1.091 (0.875-1.360)	0.442
Uric acid (1 $\mu\mu$mol/L increase)					1.001 (0.999-1.004)	0.307	1.001 (0.999-1.004)	0.301
Cold ischemia time (1-h increase)							1.001 (0.947-1.058)	0.966
Tac level (1 ng/mL increase)							0.977 (0.900-1.060)	0.574

Table 4-14. Multivariable analysis of possible risk factors for hypertension at 12 months post-transplantation (after multiple imputation)

	Model 1 AOR (95%CI)	*P*-value	Model 2 AOR (95%CI)	*P*-value	Model 3 AOR (95%CI)	*P*-value	Model 4 AOR (95%CI)	*P*-value
Recipient and donor factors								
Age of recipient (1-year increase)	1.021 (1.000-1.043)	0.055	1.014 (0.991-1.037)	0.243	1.018 (0.994-1.043)	0.150	1.017 (0.993-1.042)	0.166

Gender of recipient
  Female
  Male
	Ref
	2.235
	(1.345-3.713)
		0.002	Ref
			2.355
			(1.396-3.973)
				0.001	Ref
					1.950
					(1.114-3.416)
						0.019	Ref
							2.048
							(1.161-3.614)
								0.013

BMI at the time of KTx <25 ≥25	Ref 1.461 (0.872-2.447)	0.150	Ref 1.344 (0.786-2.296)	0.280	Ref 1.263 (0.729-2.189)	0.405	Ref 1.216 (0.697-2.123)	0.491

Prior KTx
  No
  Yes
			Ref
			0.528
			(0.271-1.031)
				0.061	Ref
					0.524
					(0.264-1.042)
						0.066	Ref
							0.509
							(0.254-1.021)
								0.057

History of HT
  No
  Yes
			Ref
			1.232
			(0.611-2.485)
				0.560	Ref
					1.203
					(0.589-2.457)
						0.612	Ref
							1.208
							(0.589-2.476)
								0.606

Steroid use
  No
  Yes
			1.639
			(0.843-3.189)
				0.145	1.854
					(0.933-3.684)
						0.078	1.869
							(0.937-3.731)
								0.076

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Cont.

	Model 1 AOR (95%CI)	P-value	Model 2 AOR (95%CI)	P-value	Model 3 AOR (95%CI)	P-value	Model 4 AOR (95%CI)	P-value
Age of donor								
<50			Ref	0.343	Ref	0.343	Ref	0.326
≥50			1.309 (0.751-2.282)		1.319 (0.744-2.337)		1.334 (0.751-2.371)	
Gender of donor								
Female			Ref	0.779	Ref	0.656	Ref	0.616
Male			0.928 (0.551-1.563)		0.884 (0.514-1.520)		0.870 (0.505-1.499)	
Hypertensive donor								
No			Ref	0.263	Ref	0.313	Ref	0.299
Yes			1.427 (0.765-2.661)		1.396 (0.729-2.671)		1.415 (0.734-2.726)	
Type of donor								
Living					Ref	0.540	Ref	0.784
Deceased					1.435 (0.452-4.554)		1.205 (0.318-4.565)	
LDL (1 mmol/L increase)					0.836 (0.645-1.085)	0.178	0.838 (0.644-1.089)	0.187
Triglyceride (1 mmol/L increase)					0.954 (0.798-1.141)	0.605	0.947 (0.787-1.139)	0.563
Uric acid (1 $\mu\mu$mol/L increase)					1.004 (1.000-1.007)	**0.030**	1.004 (1.000-1.007)	**0.033**
Cold ischemia time (1-h increase)							1.021 (0.965-1.080)	0.475
Tac level (1 ng/mL increase)							0.952 (0.854-1.062)	0.381

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5   Discussion

The findings of the present study highlight the importance of recipient and donor factors as a predictor of arterial HT in KTR.

In the current study, we detected strong evidence of an association between the male gender and post-transplant HT. Similar findings from previous studies have also been noted (Campistol *et al*, 2004; Béji *et al*, 2007; Yu *et al*, 2016). A complex set of pathways and factors can contribute to sex differences in HT. A growing body of evidence indicates that men exhibit higher levels of expression and physiological responses to classical RAAS activation, whereas females exhibit higher levels of expression and physiological responses to non-classical RAAS activation (Sullivan, 2008; Zimmerman and Sullivan, 2013; Leete *et al*, 2018). In addition, a greater expression of angiotensin type 2 receptor in females is dependent on estrogen in comparison with males (Pessôa *et al*, 2015). Furthermore, researchers have found that estrogen is capable of exerting various cardiovascular effects, including vasorelaxation, sympatho-inhibition, and preventing vascular remodeling, as well as reducing aortic stiffness by acting on endothelium and smooth muscle cells, which all play a protective role in HT (Orshall and Khalil, 2004). We proposed that these elements might partially contribute to the observed sex differences in HT. It is important to acknowledge that several other factors can play a role, including the use of healthcare services, adherence to hypertensive treatments, and behavioral factors (Santosa *et al*, 2020). Therefore, it is obvious that further research should be done on the pathways and components that result in the sex differences for HT following KTx.

Yu *et al*. (2016) described a strong association between donor HT and post-transplant HT. Our study also confirms that donor HT was independently associated with a higher risk for post-transplant HT. Possible explanations for this may be subtle nephron damage due to hyperfiltration, which may result in decreased nephron mass. However, a single-center retrospective study was unable to detect a meaningful correlation between donor HT and recipient renal function after 3 years of follow-up (Dienemann *et al*, 2019).

There is controversy over the significance of the donor's gender in the emergence of arterial HT after KTx. In a study by Pérez Fontán *et al*. (1999), the female gender showed a weak association with post-transplant HT. However, Yu *et al*. (2016)

described an association between the male gender and HT after KTx. Our study couldn't find any association between the donor gender and the development of HT. This finding was in line with a similar study as well (Béji *et al*, 2007).

Despite our study's finding that donor age was not a significant risk factor for post-transplant HT, other studies have found it to be a predictive factor. This may be explained by the different study populations, adjusted covariates, and smaller sample size in our study. For example, Pérez *et al*. (1999) showed donor age >60 years was a predictor of HT after KTx. Another study with 280 participants described donor age as a risk factor for post-transplant HT only in univariate analysis (Béji *et al*, 2007). Overall, we cannot rule out the possibility that donor age influences post-transplant HT since older kidney donors tend to have fewer functioning glomeruli.

To the best of our knowledge, this is the first study describing an association of UA as a risk factor for HT in KTR. Our results are in line with previous studies in the general population that found high serum UA levels to be associated with a higher risk of HT (Kuwabara *et al*, 2018). Future research must be conducted to verify this finding in KTR. Different conditions can lead to the elevation of serum UA levels after KTx, including immunosuppressive drugs, the presence of cystic diseases (especially autosomal dominant tubulointerstitial kidney disease and autosomal dominant polycystic kidney disease), poor graft function, and the use of diuretics (Folkmane *et al*, 2020). In a study of 155 renal transplant recipients, it was shown that both CsA and Tac increased the serum UA level (Kanbay *et al*, 2005). The possible pathophysiological mechanisms by which hyperuricemia causes HT are activation of RAAS, reducing endothelial NO, up-regulation of aldose reductase, mitochondrial dysfunction, and inflammation as a result of urate crystal deposition in the urinary lumen and endothelium of arteries (Lanaspa *et al*, 2020).

This study had several limitations. First, as this was a retrospective cohort study, we cannot determine causal associations. Second, our study was based on HBPM and not ABPM. Third, the sample size was relatively small, including individuals from only a single center. Another potential source of bias can be the definition of HT in our study which was solely based on SBP and DBP, irrespective of antihypertensive medications. Finally, there may be residual confounding factors such as LBW and PTH that we couldn't adjust for them.

Future research on HT following KTx should concentrate on the management of HT as well as the impact of LBW, PTH, and UA.

6   Conclusion and future studies

The prevalence of HT is high among KTR. Our study suggests male gender, hypertensive donor, and UA level are the potential predictors of HT after KTx. Further studies are needed to determine the risk factors of HT in this population.

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