



## Acute kidney injury and the compensation of kidney function after nephrectomy in living donation

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**Specialty type:** Transplantation

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Eccher A, Italy;  
Papadopoulos VP, Greece

**Received:** January 16, 2022

**Peer-review started:** January 16, 2022

**First decision:** March 16, 2022

**Revised:** March 27, 2022

**Accepted:** August 6, 2022

**Article in press:** August 6, 2022

**Published online:** August 18, 2022



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### Abstract

Acute kidney injury (AKI) incidence is growing rapidly, and AKI is one of the predictors of inpatient mortality. After nephrectomy, all the patients have decreased kidney function with AKI and recover from AKI. However, the characteristic and behavior of AKI is different from usual AKI and compensatory kidney function has been well known in the postoperative setting, especially in living donors. In this review, we have focused on the compensation of kidney function after nephrectomy in living donors. We discuss factors that have been identified as being associated with kidney recovery in donors including age, sex, body mass index, remnant kidney volume, estimated glomerular filtration rate, and various comorbidities.

**Key Words:** Acute kidney injury; Kidney transplant donor; Compensation; Kidney function

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**Core Tip:** Acute kidney injury (AKI) incidence is growing rapidly, and AKI is one of the predictors of inpatient mortality. The characteristic and behavior of AKI is different from usual AKI and compensatory kidney function has been well known in the postoperative setting, especially in living donors. In this review, we have focused on the compensation of kidney function after nephrectomy in living donors. We discuss factors of compensation of kidney function after nephrectomy.

**Citation:** Okumura K, Grace H, Sogawa H, Yamanaga S. Acute kidney injury and the compensation of kidney function after nephrectomy in living donation. *World J Transplant* 2022; 12(8): 223-230

**URL:** <https://www.wjgnet.com/2220-3230/full/v12/i8/223.htm>

**DOI:** <https://dx.doi.org/10.5500/wjt.v12.i8.223>

## INTRODUCTION

The incidence of acute kidney injury (AKI) is growing rapidly in many situations[1]. Despite advances in medical care, AKI remains an independent predictor of in-hospital mortality[2]. While the nature of kidney is the organ to recover, it is well established that AKI, especially when severe, is a risk factor for incident and progressive chronic kidney disease (CKD) and eventually leading to progressive nephron loss and end-stage renal disease (ESRD)[3,4].

Kidney transplantation has been considered a preferred treatment for patients with ESRD and offers a better quality of life than dialysis[5,6]. While a previous study showed that living donation of kidney is safe in a large cohort, nephrectomy is a major procedure which is associated with potential risks for the donor, including increased cardio-vascular risks and progression to ESRD in the long-term [7]. After donation of the kidney, it has been well known that all patients have hemodynamic changes associated with AKI and have compensated kidney function with the contralateral kidney after donation[6,8-12]. The degree of contralateral kidney function has been reported to be around 60%-70 % on average in previous studies[13,14], however, the degree of compensatory kidney function varies in each donor. In this review, we have discussed the topics related to the clinical factors of compensation and the mechanism of recovery after kidney donation.

## CLINICAL FACTORS

Many variables are involved in the clinical settings for kidney recovery after kidney donation (Table 1, Figure 1). Age is one of the significant factors which affects the extent of recovery. Younger age is associated with favorable outcomes in many studies[6,8,15-19] and this is supported by the facts that aging is associated with underlying abnormalities and structural changes such as nephrosclerosis and nephron hypertrophy[16]. The rate of glomerular density has an inverse correlation with aging[20]. The number of nephrons decreases with aging and affects the function of the kidney[20]. Denic *et al*[21] investigated the risk factors associated with kidney abnormalities, and they demonstrated that mild hypertension and aging are associated with underlying abnormalities. They showed the changes of the volumes of kidney, cortex and medulla in living kidney donors[22].

Hypertension is also one of the significant factors which affect the extent of recovery in kidney function[6]. It is known that prevalence of hypertension increases with age. Hypertension was previously regarded as contraindication for living kidney donation, however, living donor donation was reported to be safe if hypertension is under controlled with medication[22]. On understanding of kidney aging, kidney function in people with advanced age have less reserve when they tend to develop CKD and have also higher risk of AKI[23]. As people get old, the prevalence of hypertension also increases, and glomerular hypertrophy has been identified as an integral feature of hypertensive nephropathy and seems to precede rather than to compensate for glomerulosclerosis[24].

Gender is another significant factor for kidney compensation and prognosis. Male gender is associated with poor prognosis in kidney donation[6,8,15], however, this is controversial since many studies showed that gender did not reach to conclusion as one of the independent factors[17,25,26]. This might be more related to the fact that male gender has a higher rate of smoking, which is one of the factors affecting the kidney function and is associated with hypertension.

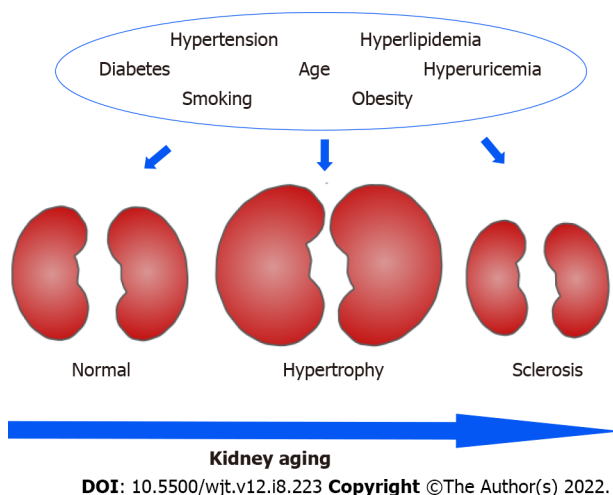
Metabolic syndrome has been defined by the National Cholesterol Education Program Adult Treatment Panel III if three or more of the following five criteria are met: Waist circumference over 40 inches (men) or 35 inches (women); blood pressure over 130/85 mmHg; fasting triglyceride level over 150 mg/dL; fasting high-density lipoprotein cholesterol level less than 40 mg/dL (men) or 50 mg/dL (women); fasting blood sugar over 100 mg/dL[27]. Metabolic syndrome has been shown to have a negative impact on remnant kidney function after nephrectomy since metabolic syndrome is associated with a high incidence of hypertension, obesity, hyperglycemia, and hyperuricemia[17,28,29].

The impact of serum uric acid level has been an emerging topic on the residual kidney function in living kidney donors. The total 4650 living-donor cohort study showed that donors with post-donation gout had higher risk of developing AKI and progression to CKD[30]. Other living-donor studies from Turkey and Korea also suggested that preoperative hyperuricemia are associated with impaired postoperative renal function at 6 and 12 mo[31-33]. It was also reported that preoperative hyperuricemia was strongly associated with suboptimal renal compensatory function or recovery at one year after renal donation[34]. Furthermore, hyperuricemia had 1.76-fold higher adjusted risk of adverse events

**Table 1 Clinical factors associated with kidney recovery in living donors**

Ref.	Significant factors		
Ohashi <i>et al</i> [17]	Age	Presence of metabolic syndrome	Chronic histological changes
Ibrahim <i>et al</i> [8]	Age	Sex	BMI
Rook <i>et al</i> [11]	Age	BMI	
Denic <i>et al</i> [21]	Age	HTN	
Shiraishi <i>et al</i> [15]	Age	Sex	BMI
	HTN		
Nishida <i>et al</i> [34]	Hyperuricemia	Chronic histological changes	
Yakoubi <i>et al</i> [25]	Age	BSA adjusted RKV	Preoperative eGFR
Shinoda <i>et al</i> [26]	BMI	RKV/BSA	
Okumura <i>et al</i> [6]	Age	Sex	History of HTN
	RKV/Wt		
Zabor <i>et al</i> [18]	Age	Sex	History of HTN
Lee <i>et al</i> [19]	Age	Sex	History of HTN
	BMI	History of DM	Preoperative eGFR
	RKV		
Vaz <i>et al</i> [42]	Age	Sex	

BMI: Body mass index; HTN: Hypertension; BSA: Body surface area; RKV: Remnant kidney volume; eGFR: Estimated glomerular filtration rate; CrCl: Creatinine clearance; mGFR: Measured glomerular filtration rate; Wt: Weight; DM: Diabetes.

**Figure 1 Clinical factors associated with kidney compensation.**

within 5 years after donation, such as cardiovascular events, initiation of dialysis, and *de novo* prescriptions for hypertension, hyperuricemia, diabetes, and dyslipidemia as well as lower estimated glomerular filtration rate (eGFR)[35].

The size of kidney is one of the important factors affecting the donor/recipient outcomes in kidney transplantation[36,37]. Since larger size of the kidney is associated with better renal function, it is recommended to choose the smaller kidney for donation to fulfil the principle of leaving the “better” kidney in donor if there is a more than 10% volume difference between kidneys in donor. The reasons to select suboptimal side of kidneys in donation, were cysts or tumors (46.5%), arterial abnormalities (22.7%), inferior size or function (19.8%), and anatomic abnormalities (11.0%), and those kidneys showed worse long-term overall graft survival regardless of the reasons[38].

Remnant kidney volume (RKV) in living donor is one of the important factors to determine the kidney recovery after donor nephrectomy[6,19]. Shinoda *et al*[26] showed the ratio of RKV to body

surface area (BSA) ratio has an independent factor to predict renal function or compensation after kidney donation. Yakoubi *et al*[25] also showed BSA adjusted with RKV was an independent predictor of kidney recovery after donation. With respect to recipient outcomes, the ratio of donated kidney volume to body weight (Wt) has been suggested as an important factor related to allograft function[39].

The ratio of RKV to Wt (RKV/Wt) was reported to be one of the significant associated factors in eGFR at 1 year after kidney donation[6]. Although it has been thought that a lower RKV/Wt can cause hyperfiltration and subsequent proteinuria[40], Song *et al*[41] suggested that a ratio of RKV/Wt less than 2.0 mL/kg did not affect the eGFR in donors but was associated with more severe proteinuria at 1 year after donor nephrectomy. There was no significant difference in the RKV/Wt ratio in the study [41], but they suggested the “deterioration” of kidney function since the donors were associated with presence of proteinuria at 1 year after donation. Thus, a lower RKV/Wt ratio might be associated with hyperfiltration and subsequently decrease “renal reserve”.

Laterality of the donated kidney is another factor to evaluate when considering donor and recipient outcomes in kidney transplantation. Vaz *et al*[42] studied the outcomes of hand assisted laparoscopic donor nephrectomy (HALDN) of the left and the right kidney among 739 donors. This study concluded that, although most transplant centers and surgeons prefer performing left nephrectomies because of having a longer vein, right HALDN nephrectomy is a safe procedure with similar outcomes to left HALDN. Gunseren *et al*[43] compared right and left side laparoscopic donor nephrectomy outcomes and found that they had similar intraoperative outcomes. These authors noted, however, that dissection of lymphatic structures during left laparoscopic donor nephrectomy may cause chylous drainage and prolong hospitalization time compared to right-sided nephrectomy. Zeuschner *et al*[44] evaluated left and right pure laparoscopic donor nephrectomies and found a higher rate of complications for recipients of right grafts, but long-term function and graft survival were equivalent.

## PATHOLOGICAL CHANGES OF NEPHRECTOMY

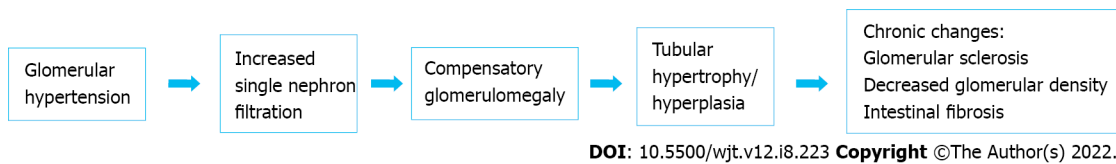
After the nephrectomy, the compensation of contralateral kidney function has been well known. Immediately after nephrectomy, an approximately 40% increase in renal plasma flow and glomerular filtration rate is measured in the remaining kidney[9,45]. This leads to developing glomerular hypertension and increased single-nephron filtration with compensatory glomerulomegaly. The glomerulomegaly from hyperfiltration also occurs in response to nephron loss. In addition to glomerulomegaly, hyperfiltration leads to tubular hypertrophy and hyperplasia. Prolonged hyperfiltration and glomerular hypertension causes glomerular sclerosis and decreased glomerular density (Figure 2).

Once glomerular size reaches a certain threshold, glomerular sclerosis, hypertension, proteinuria, and renal failure may develop[46]. This pathological process was associated with kidney function, blood pressure and metabolic conditions: Metabolic syndrome, hypertension, hyperglycemia and hyperuricemia[17,20,34,47,48]. However, these histological changes might not always be seen in donors since donors were in a relatively good state of health and the unaffected nephrons would respond with compensation[48]. Studies showed that donors who had hyperuricemia, had chronic histological changes such as intestinal fibrosis, tubular atrophy and arterial hyalinosis in the donated kidney[34]. Intestinal fibrosis and tubular atrophy have significant impacts on long term graft function[49]. It is thought that arteriosclerosis has a significant relationship with intestinal fibrosis and tubular atrophy since the chronic ischemic condition caused by arteriosclerosis induces histological changes such as intestinal fibrosis, tubular atrophy and glomerular sclerosis[50].

Rule *et al*[20] showed that increased GFR, body mass index and uric acid level and a family history of end stage renal disease were independent predictors of decreased glomerular density. The size of individual nephrons can reflect important elements of metabolic regulation. After living kidney donation, donors can develop glomerular hypertension and increased single-nephron filtration with compensatory glomerulomegaly[51-53]. Polichnowski *et al*[54] showed that contralateral nephrectomy is associated with kidney recovery from ischemic kidney injury and prevent tissue atrophy with capillary repair and tubule redifferentiation. This result supports that remnant kidney is not vulnerable but sustainable after kidney donation. However, we emphasize that the best strategy for AKI is prevention. It is rare to perform living donation in the setting of AKI, however, in deceased donors, Cima *et al*[55] reported that kidney transplant could be performed from donors with AKI depending on the histological grading score with glomerulosclerosis, tubular atrophy, intestinal fibrosis, vascular damage and acute tubular necrosis[55,56].

## MOLECULAR CHANGES OF NEPHRECTOMY

At present, the specific mechanism after nephrectomy remain unclear. However, several hypotheses have been proposed and it has shown that endothelial injury and recovery have an important role in the pathogenesis of kidney injury[57]. As discussed above, renal blood flow and GFR significantly increased after nephrectomy. This has been a critical role of upstream factors responsible to recruit dormant



**Figure 2** Changes in kidney after nephrectomy.

nephrons and subsequently to improve in GFR. As renal blood flow increases and renal glomerular filtrate rate increases, it would lead to increase oxygen consumption and cause tissue hypoxia. It induces hypoxia-inducible factor 1 alpha and induces vascular endothelial growth factor. Hypoxia also induces phosphatase and tension homolog in tubules which causes tubule redifferentiation and repair [54].

In another way, renal tubular epithelial cells, which are surviving from ischemic injury, undergo differentiation[58]. These surviving epithelial cells express vimentin (an intermediate filament protein, which is found in undifferentiated mesenchymal cells but not in differentiated kidney cells), and proliferating cells nuclear antigen (a marker of mitogenesis), in contrast, damaged cells do not express either vimentin or proliferating cell nuclear antigen[59]. The molecular drivers in the process of intrinsic repair remain indeterminate, but the transcription factor Sox9 has been shown to be a critical part of the cellular repairing pathway in surviving renal tubular epithelial cells[60].

Oliver *et al*[60] reported that there are renal specific stem cells, which have been identified in the renal tubules as well as the papilla, however, the contribution of these cells still remains under investigation. Many recent studies have looked into the progenitor cell or bone marrow derived mesenchymal stem cells in renal repair[61]. The mesenchymal stem cell, which are derived from renal specific or bone marrow, may accelerate the process of repairing the injured tubules by direct proliferation or through paracrine effects. In transplant kidney, some studies suggest that the recipient derived cells may repopulate injured tubule[62,63], however, mesenchymal stem cells may predominantly play a role in their beneficial effects *via* paracrine mechanisms[64]. The mesenchymal stem cells may release microvesicles to communicate between cells and protect renal injury in addition to releasing cytokines [65].

## CONCLUSION

We have performed living donor kidney transplant safely, however, a large cohort study showed that being a donor increased cardiovascular risk and progression to ESRD in the long term[7]. Since the degree of recovery from AKI affects the prognosis of kidney function[66], we believe that it is important to identify the risk of patients without compensation of kidney function of the contralateral kidney to predict the long term risk.

## FOOTNOTES

**Author contributions:** Okumura K and Yamanaga S designed the study, wrote the initial draft of the manuscript; Okumura K, Grace H, Sogawa H and Yamanaga S critically reviewed and revised the manuscript; and all authors approved the final version of the manuscript.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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**S-Editor:** Wang JJ

**L-Editor:** A

**P-Editor:** Wang JJ



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