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# Effect of Long Cold Ischemia Time of Kidneys from Aged Donors on Prognosis of Kidney Transplantation

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With the increasing incidence of end-stage renal disease (ESRD), patients' life span and life quality are significantly reduced. Kidney transplantation has gradually become the ideal method for treating ESRD, and the shortage of organ sources has become the main problem. In recent years, China has successfully realized the transformation of organ sources. Voluntary donation after the death of citizens has increased year by year, and the number of kidney transplantations has increased, which alleviates the organ shortage to a certain extent, but compared with the past, the increasing proportion of aged donors has also become an inevitable global problem. At the same time, due to the sudden and widespread distribution of voluntary donation, most donor kidneys have the problem of longer cold ischemic time (CIT). The probability of adverse events, such as delayed renal function recovery after transplantation, was also significantly increased. At present, there is little research on the effect of donor's aging and long CIT on the prognosis of renal transplantation. This paper reviews the literature in recent years and explore this problem from 2 aspects: the elderly donor and the long CIT.

**Keywords:** Aging • Cold Ischemia • Kidney Transplantation • Organ Preservation

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## Background

Although the number of voluntary organ donations increases year by year, it is still far from enough to cope with the shortage of donor kidneys. It has also become a vital exploration direction to try to relax the upper limit of donor age. There is no uniform and a strict limit on the upper limit of donor age in the world. In the past, the age of donors was generally no more than 60 years old. Those over 50 or 55 years old were defined as aged donors. Nowadays, many transplantation centers have extended the age limit of donors to 65, and even to 75 or over 80 in some centers [1-4]. Generally speaking, with population aging, even without considering the factors of diseases in the elderly, there is glomerulosclerosis caused by aging and the decrease of effective nephrons.

In addition, the incidence of donor-related diseases is increasing. However, to further alleviate the severe shortage of donors, use of organs from aged donors becoming more important. To avoid wasting donor resources and to ensure recipient quality of life as much as possible, many transplant centers have begun matching aged donors to aged recipients [1,5].

On the other hand, the uncontrolled CIT of donation after circulatory death (DCD) donor kidneys has always been a difficult problem. Research shows that longer CIT is related to delayed graft function (DGF), reduced survival rate, primary non-function (PNF), and early dysfunction of transplanted kidneys [6-12].

## Progress in Related Research on Aged Donors

### The Relative Importance of Older Donors

Until the 1990s, kidney donors of deceased donors over 55 years of age were often discarded directly [1]. With improved acquisition methods and organ evaluation, age is gradually not regarded as an independent limiting factor [13-16]. In response to the shortage of donors, in 2002, UNOS (American United Network for Organ Sharing) proposed ECDs (expanded-criteria donors). The kidneys provided by donors  $\geq 60$  years old are called ECDs, even for donors aged 50-59, if there is: 1) Death due to cerebrovascular accident, 2) Serum creatinine level is higher than 1.5 mg/dl, or 3) History of hypertension, 2 or more of which are also ECDs [17]. According to the report, the UNOS has a high abandonment rate for elderly donors. About 50% of the organs from donors over 60 years old are abandoned [18], and the abandonment rate for organs from donors over 65 years old is over 60% [1]. The abandonment rate shows the importance of donor age in organ transplantation. Of course, the high rate of kidney abandonment in the elderly is not only a UNOS problem.

In general, aged donor kidneys have less renal function reserve compared with young donor kidneys. Aged donor kidney tolerance is worse, and it is more susceptible to the effects of long CIT and ischemia-reperfusion injury (IRI) [19, 20]. As a result, many uremic patients and even doctors do not want aged donor kidneys.

### Clinical Application Effect of Aged Donor Kidneys

Although the aged donor kidneys are inferior to young donor kidneys in the same situation, it does not mean that they have no value. It is not uncommon for elderly patients to benefit from aged donor kidney transplantation [1-4]. It is not advisable to rely solely on age to determine whether the donor's kidney is usable.

In Europe, as early as 1999, Eurotransplant launched the "Eurotransplant senior program" (ESP), which can be simply understood as a program of "old donor matching old recipient". The donors and recipients in this program were all over 65 years old, and they did not focus on HLA matching, mainly to meet the requirements of ABO blood group matching and negative cross-matching. Another characteristic of ESP is local distribution, which can significantly reduce the donor kidney's cold ischemia time. ESP shows quite good feasibility [21].

In a study by Jozwik et al [2], the donor kidneys aged  $\geq 70$  years (the study group) were compared with the donor kidneys aged  $\leq 69$  years (the control group). The average ages of donors in the study group and the control group was 75 and 45 years old, respectively, and the average age of recipients were 65 and 48 years old, respectively. Other indexes such as BMI and serum creatinine level were similar. The incidence of DGF, 3-year survival rate of the donor kidney, mean serum creatinine level, and EGFR were compared. The study showed that although the control group's results were slightly better than in the study group, there was no statistically significant difference, and everything was within the acceptable range. There are many similar conclusions to this study [22-26].

Collini et al [27] studied the incidence of postoperative complications in patients receiving kidneys from donor  $\geq 75$  years. Compared with the control data, the situation was slightly worse but still acceptable.

There are several recent reports on elderly donors [28-32], generally showing no breakthrough research results. In recent reports, the number of cases included in the study increased, and some studies even included many cases of donors over 80 years old [28,30]. For example, 22.5% of renal transplant donors in research [28] were over 80 years old, 128 renal transplant donors in the study [30] were more than 80 years old, and 1084 renal transplant donors were between 60 and 79 years old.

Therefore, as long as the aged donor kidney is appropriately evaluated, allocated, and used, use of kidneys from aged donors can produce acceptable results. Some studies have even proved that aged donor kidneys can be successfully transplanted to recipients over 40 years old [33,34]. Needless to say, compared with the elderly patients who choose to continue dialysis and wait for “high-quality donor kidneys” in the same condition, the survival opportunity and quality of life of the elderly patients who receive the elderly donor kidneys are much higher [1-4].

### How to Reduce the Risk of Using Aged Donor Kidneys

Although many studies have shown that aged donor kidneys can be used, compared with young donor kidneys, there is an inherent higher potential risk, so ensuring its safety and effectiveness is undoubtedly very important. There is a kind of transplantation scheme, which is to transplant 2 deficient donor kidneys to the same recipient, to avoid discarding the donor kidneys and make up for the lack of single-kidney supply at the same time. However, it is clear that not every aged donor kidney is a “defective product”. If all the aged donor kidneys are treated in such a “double-kidney transplantation” way, it would inevitably cause many donor kidney losses. Therefore, it is essential to evaluate the quality of the donor kidney before an operation. A good-quality aged donor kidney is enough for “single-kidney transplantation”.

#### eGFR Assessment

Snanoudj et al [35] used the donor eGFR calculated by the Cockcroft-Gault formula. Donor kidneys with eGFR >60 mL/min were used for “single-kidney transplantation”, donor kidneys with eGFR at 30-60 mL/min were used for “double-kidney transplantation”, and donor kidneys with eGFR <30 mL/min were discarded. The age of recipients studied was over 65 years. According to their findings, donor eGFR is a simple and effective criterion. However, some scholars believe that the donor’s creatinine value does not always reflect the real situation and the calculated eGFR reliability is debatable [36].

#### Preoperative Biopsy

Preoperative biopsy of the aged donor kidney is considered as a reliable assessment method by most scholars. The difficulty is that many transplant centers are not equipped with 24-h standby pathologists, which makes it challenging to carry out the routine biopsy of aged donor kidneys. On the other hand, the biopsy results will affect the subsequent organ allocation, and the time it requires can greatly prolong the cold ischemia time [25]. For the application of preoperative biopsy, many studies have put forward their views. It is more common to take a certain age as the boundary (for example, 60 years

old). If the boundary value is exceeded, all patients will be given a preoperative biopsy. But some studies found that such an approach is too broad and may waste medical resources. They advocate further combining of clinical data to determine whether a preoperative biopsy is necessary.

The advantage of combining clinical data lies in the ability to classify the aged donor kidneys first. The need for biopsy was determined by age, known clinical risk factors (eg, creatinine clearance rate, proteinuria, hypertension, diabetes), and preoperative imaging results. Then, the biopsy results were graded and assigned according to their respective “scoring system”.

Taking an Italian study [36] as an example, the researchers advocated that the elderly donors should be divided into 2 layers: one layer aged 60-69 and one layer aged  $\geq 70$ . If there are no clinical risk factors (including  $\text{EGFR} \leq 60$  ml/min calculated by Cockcroft-Gault formula; proteinuria  $\geq 1$ g/day; simultaneous use of  $\geq 2$  antihypertensive drugs for hypertension; diabetes mellitus and cardiovascular complications), 60-69-year-old patients can be directly allocated for single-kidney transplantation. If there are  $\geq 1$  clinical risk factors, a preoperative donor kidney biopsy is required. If there are  $\geq 70$ -year-old patients, regardless of whether there are clinical risk factors, biopsies are needed. According to the scoring method [37] published by Remuzzi, the total score is 12 points: 0-3 points can be used for single-kidney transplantation, 4-6 points can be used for double-kidney transplantation, and if more than 7 points, the organ can be discarded. This study shows that this method is safe, effective, and easy to carry out in daily work.

In general, many scholars have summed up a set of their standards [37-40], each with its advantages and disadvantages, for use of elderly donor kidneys in single-kidney transplantation, double-kidney transplantation, or directly discarded. Although there is no universally recognized “perfect standard”, these pioneering achievements lay a good foundation for future research. Here are 2 scoring methods related to preoperative biopsy, which are discussed below.

#### Remuzzi Score

This scoring system’s total score is 12 points, which comes from 4 aspects, each accounting for 3 points: glomerulosclerosis, tubular atrophy, interstitial fibrosis, and stenosis of arteries and arterioles. It is worth mentioning that this method generally does not recommend using frozen section (FS) for examination. The FS approach may lead to underestimation of arteriolar hyalinization and glomerulosclerosis, as well as overestimation of acute tubular injury and interstitial fibrosis [41], with high technical requirements for pathology staff. Most reports used a 16-gauge puncture needle to sample the upper pole or lower pole of the donor kidney, and some used

wedge-shaped sampling, which requires no less than 25 glomeruli. After that, they were fixed in formalin solution, embedded in microwaved paraffin, cut into 5- $\mu$ m-thick sections, and then stained with HE, Schiff iodate, Masson, and Van Gieson stains. The whole process can be completed in about 3 h [36] if properly managed and it will not have a significant impact on CIT.

#### MAPI (Maryland Aggregate Pathology Index)

Unlike the Remuzzi score, the MAPI needs to evaluate 5 aspects: arteriolar hyalinization (4 points), periglomerular fibrosis (4 points), arterial wall-to-lumen ratio higher than 0.5 (2 points), global glomerular sclerosis in more than 15% of glomeruli (2 points), and interstitial scar (3 points), with a total score of 15 points. It is generally considered that organs receiving more than 7 points are not suitable as donor kidneys. The advantage of the MAPI score is that the requirements for pathology staff are relatively lower. Although paraffin section examination is better, FS is also feasible, with promising results [42].

There are other reports on the application of Banff classification to scoring [43]. The score includes 7 aspects, and it seems to work well.

In summary, donor age is an essential and seemingly less important indicator, and many want to know what the maximum acceptable age is. Unfortunately, the current literature reports cannot give a definite answer. Perhaps an upper limit does not exist for the existing human life span. After all, kidney transplants over the age of 80 have had many successful precedents [4]. It seems that how to optimize the preoperative evaluation of aged kidney donors is more necessary and practical.

## Research Progress of CIT

Unlike parental kidney transplants, donated kidney transplants have been faced with the challenge of minimizing CIT. As a well-known risk factor, CIT has been extensively studied in the field of kidney transplantation. However, there is still no consensus on its precise relationship with the outcome of transplantation.

### Common Effects of CIT on the Transplanted Kidney

#### DGF

It is generally accepted that too-long CIT is an important determinant of DGF [44,45].

Investigation of Irish et al [6] was a multivariate logistic regression analysis that included 24 337 recipients of deceased donor kidney transplants between 2003 and 2006. The most

significant factors associated with DGF were CIT, donor creatinine, BMI, cardiac death donor, and donor age.

Other paired study designs compared 2 kidneys from the same donor source and can largely remove some donor-related confounding factors. A paired study concluded that too-long CIT (>15 h in the study) resulted in a 1.5-fold increase in the incidence of DGF [46]. Doshi et al conducted a multivariate analysis of 5382 recipients in the United States UNOS and found that longer CIT (22 h vs 20 h) was associated with the occurrence of DGF [47].

Many studies have explored the relationship between CIT and DGF [32,48-54]. It is generally felt that there is a certain threshold value for CIT, and once exceeded, the risk of DGF will increase significantly. Some studies indicate that every additional hour of CIT carries additional risk of developing DGF, even when the CIT is very short [7].

#### AR (Acute Rejection)

Whether there is a relationship between CIT and AR is controversial at present. A study of 14 000 kidney transplants with ECDs found no relationship between these 2 factors [46]. In contrast, a study of 611 kidney transplant recipients reported that AR incidence increased with increased CIT [12]. A recent report analyzed a total of 63 798 deceased donor kidney transplants from 2000 to 2010 in the OPTN database (Organ Procurement and Transplantation Network database), and also found that the increase of CIT was associated with an increased risk of developing AR [55], especially showing the difference in risk between the 2 groups with CIT <12 h and CIT <24 h.

#### Graft Loss

Like AR, the relationship between CIT and graft loss, or graft survival, is also controversial. Some suggest that the influence is not significant [45,46,56,57], while others think that CIT is the main influencing factor [10,12,48,58]. It is worth mentioning that most studies set different thresholds, which may also impact the results of the study. For example, in Salahudeen et al's study, the survival rate of kidney donors with CIT >30 h was significantly reduced [10], while in Opelz et al's study, CIT up to 18 h did not cause an increased risk of graft loss [58].

Unlike previous grouping studies based on cut-off values, a newer study [11] showed that every 1 h increase in CIT increased the risk of graft loss (hazard ratio, 1.013). For example, recipients with a CIT of 12 h had an 8% higher rate of graft loss than recipients with a CIT of 6 h, and a CIT of up to 30 h had a nearly 40% higher rate of graft loss than in recipients with a CIT of 6 h.

## CIT and Different Organ Preservation Methods

Today, the 2 most commonly used organ preservation methods are simple cold storage (SCS) and hypothermic machine perfusion (HMP). Based on the simplicity and ease of SCS, most centers use this method to preserve the donor kidney to be transplanted. On the other hand, although HMP requires valuable equipment and much higher human and material investment than SCS, HMP can monitor multiple indicators during perfusion, facilitating the assessment of preserved organs. It is generally believed that HMP is superior to SCS in preservation effect. There are also many reports comparing HMP with SCS, which suggest that the incidence of DGF in HMP is lower, and the long-term survival rate of grafts is higher [59-63].

It seems reasonable that the transplanted kidney can be “effectively preserved” for a longer time in the way of HMP preservation, but in fact, is this the case? Longer storage time means longer CIT. When the storage time is long, can HMP protect the kidney effectively?

Gill et al conducted a study and analysis of recipient data on SRTR (Scientific Registration of Transplant Recipients) [64]. The researchers first divided the data into 3 groups according to normal standard donors (SCD), expanded standard donors (ECD) and donors after circulatory death (DCD). Then, according to the length of CIT, each group was divided into a 0-6 h group, a 6-12 h group, a 12-18 h group, an 18-24 h group, a 24-30 h group, a 30-36 h group, and a >36 h group, and compared the effects of HMP and SCS. The results showed that HMP had a lower incidence of DGF than SCS in the whole SCD group, all ECD groups with CIT >6 h, and all DCD groups with CIT at 6-24 h. Although HMP is superior to SCS to some extent, CIT is still an independent risk factor for DGF regardless of the preservation method, which needs to be shortened as much as possible.

In another recent study [65], both sides of the same donor's kidneys were preserved by HMP and SCS, respectively. According to the length of CIT, they were divided into a <10 h group, a 10-15 h group, a 15-20 h group, and a >20 h group. The results showed that the incidence of DGF in the HMP group was significantly lower than that in the SCS group under the condition of <10 h; the other groups' results were not statistically different. It was concluded that when CIT is not long, HMP can have a significant advantage, and even if HMP is used for preservation, CIT is still an independent risk factor for DGF.

Thus, different preservation methods can reduce the potential threat of CIT to the transplanted kidney to some extent, but it does not mean that this threat can be eliminated. It is still necessary to shorten CIT as much as possible.

## Kidneys from Older Donors Have Long CITs

As mentioned earlier, aged kidney donors are less tolerant and more susceptible to long CIT and ischemia-reperfusion injury [19,20]. When the 2 risk factors of aged and CIT are superimposed, the problem will undoubtedly become more complex. It is likely that all clinicians want to know at what age and at what duration of CIT should donor kidneys be abandoned? There are too many influencing factors in real-life cases, and it is impossible to give a definite answer through data analysis of clinical cases. This paper can only attempt to summarize some studies that include both “aged” and “CIT” data, and draw on these successful cases to answer vaguely at what age and at what duration of CIT should a donor kidney be discarded.

In a 2006 report [25], a total of 62 patients received kidney transplants from donors after brain death (DBD) aged >60 years: 8 received single-kidney transplants and 54 received double-kidney transplants. The overall donor age was  $69\pm 8$  years, CIT was 18 (15-20) h, and the follow-up was 24 (13-36) months. It has been demonstrated that donors over age 60 can still provide excellent graft function for up to 3 years.

In another related study of DBD aged  $\geq 80$  years [4], 74 kidneys donated by 37 donors were used for “single-kidney transplantation” and “double-kidney transplantation” according to preoperative evaluation. The donors were all White, with an age range of 80-86 and a CIT of 16 (13-18) h. Of the 37 recipients who underwent transplantation, 2 needed to be converted to dialysis after surgery and 2 died with successful renal transplantation. It was demonstrated that after good preoperative evaluation, donors over 80 years of age can still provide good graft survival and function for up to 7 years.

Therefore, as long as proper preoperative means of assessment are used, CIT of aged DBD up to 18 h is completely acceptable [4,25,27].

Unfortunately, no such direct studies of DCD kidney transplantation in the elderly have been published. In an earlier report [43], DCD kidney transplantation in 1994-2005 was studied. In the study group (>60 years old), the donor age was  $65\pm 4$  years, the CIT was  $25\pm 6$  h, the patient survival rates at 1 and 5 years after surgery were 94% and 83%, respectively, and the graft survival rates at the time of death were 67% and 52%, respectively. Such results do not seem to be ideal, but it is worth mentioning the following: 1) The study was conducted more than 10 years ago, and the intervening years of advances in transplant technology and drug development are likely to improve such outcomes; 2) Only 58% of donors underwent preoperative biopsies, and the scores after biopsy and organ allocation were not detailed in the report. It is also possible that outcomes will improve if there was a better preoperative biopsy,

scoring scheme, and carried out single-kidney transplantation or double-kidney transplantation, respectively.

Since DCDs experience warm ischemia, it is generally accepted that kidney transplantation from DBDs is more effective than kidney transplantation from DCDs. Although DCDs are increasing year by year, in countries with brain death legislation, DBD still dominates [66,67]. Due to the few transplantation cases available for research and the significant risk of exploration, there will inevitably be few studies on aged DCD kidney transplantation.

However, it is worth mentioning that kidney transplantation from DCDs is no worse than that from DBDs when the warm ischemia time can be strictly controlled [66,67]. Although aged donors were not the main focus of these 2 large studies, they suggest that even with a relatively long CIT, elderly DCD kidneys may be well suited for transplantation when warm ischemia time is strictly controlled.

## Conclusions

Regardless of age or CIT, a single factor should not be a determinant of discarding the donor kidney directly. Full consideration needs to be given to the evaluation of the function and structure of the donor kidney. There are undoubtedly many shortcomings in the summary and review of this paper, as follows. 1) References are all related reports from outside China. Chinese reports on aged donors focus on living donor kidney

transplantation. The CIT of such kidney transplantation is generally very short, which is relevant to our study. 2) The existing reports on kidney transplantation of aged donors mainly focus on DBD. The conclusions obtained are certainly not broadly representative, especially for countries without brain death legislation, and may not be of great use for reference. 3) Most of the large-scale research reports originate from Europe and the United States. Whether ethnic differences have an important effect is unknown. Despite these shortcomings, the present report still has some interesting results. Kidneys transplanted from aged DBDs can of acceptable quality even if the CIT is relatively long (up to 18 h).

Further optimization of the preoperative evaluation program is essential. According to each transplantation center's actual situation and referring to the existing biopsy scoring system, careful attempts can be made gradually in clinical practice. For aged DCDs, more caution is needed due to the lack of sufficient direct evidence. On the other hand, ensuring more effective preservation of the donor kidney within a specific period is also worth exploring. In addition to clarifying the advantages and disadvantages of common organ preservation methods, is there a better choice? Or is there some way to prevent or even reverse some damage during organ preservation? These topics warrant further research in future studies.

## Conflict of Interest

None.

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