의학석사 학위논문

60 세 이상 고령의 뇌사 기증 신장 이식시 심장 질환, 뇌혈관질환 여부가 이식 후 환자에게 미치는 영향을 이식 대기자와 비교 분석

Comparative Analysis of the Impact of Cardiac and Cerebrovascular Diseases on Post-Transplant Patients in Deceased Donor Kidney Transplantation for Individuals Aged 60 and Above, Compared to Transplant Waitlist Candidates

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Abstract

Background

As life expectancy increases, there is a rising prevalence of kidney transplantation and elderly patients on dialysis waiting lists. This study aims to compare the survival rates of elderly individuals (aged 60 and above) undergoing kidney transplantation with those on the waiting list.

Methods

This retrospective analysis, conducted at Asan Medical Center (AMC), includes elderly patients aged 60 and above who underwent their initial deceased donor kidney transplant between January 2008 and December 2022. Recipient and candidate characteristics, along with transplant-related factors, were analyzed.

Results

Comparison of survival rates between the transplant and waitlist groups revealed a trend towards better long-term survival in the transplant group, although statistically insignificant. Further stratification based on the presence of cardiac and cerebrovascular accidents and age (before and after 65) was conducted. Patients under 65 in the transplant group without comorbidities exhibited a tendency towards better survival. In those aged 65 and older without comorbidities, a favorable trend in long-term survival was observed, albeit not statistically significant. However, the transplant group with comorbidities showed unfavorable survival rates compared to the waitlist group.

Conclusions

This study indicates an inclination towards improved survival rates in elderly kidney transplant recipients. Nevertheless, especially in elderly individuals with comorbidities, transplantation may pose higher risks than dialysis. Thus, transplant centers should develop tools to assess internal survival rates and risk profiles of local dialysis patients. These efforts are crucial for enhancing survival rates among the elderly and optimizing the allocation of scarce donor kidneys.

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1. Introduction

The global incidence of end-stage renal disease (ESRD) and its associated burden are growing rapidly[1,2]. This increase is particularly notable among elderly patients. According to the US Renal Data System 2022 Annual Data Report, nearly half of all new ESRD patients worldwide are elderly patients[2]. South Korea, experiencing one of the most rapid aging processes among nations, reflects this trend noticeably. Among ESRD patients in South Korea, the proportion of elderly patients has steadily increased from 36.0% in 2010 to 51.9% in 2019[1]. This demographic shift is significant as it presents both clinical and ethical challenges in the management of ESRD, particularly regarding the suitability of elderly patients for kidney transplantation (KT).

The number of KT in elderly patients has been steadily increasing, and the outcomes of transplantations are also improving[3-7]. Consequently, KT is considered the preferred treatment option when considering quality of life and longevity for these patients. However, recipient age remains a significant factor impacting post-transplantation mortality rates and graft survival reduction[3,6,8,9]. Particularly as age increases and in cases with comorbidities such as diabetes mellitus (DM) and cerebrovascular accidents (CVAs), the safety and efficacy of kidney transplantation remain controversial[6,10-12]. Despite having a lower survival benefit compared to younger patients, it has been noted that older patients can still benefit from KT[13]. Nonetheless, assessing the benefits of KT in elderly patients is challenging, and clear guidelines are lacking[14].

The shortage of donated kidneys for transplantation has led to an increase in the number of patients on waiting lists, with associated risks of morbidity and mortality while waiting[1,2]. To address this, kidney allocation policies are being re-evaluated to balance efficiency and fairness. In the United States and Europe, policies like 'young-to-young' and 'old-to-old' allocation are being adopted to optimize the use of available kidneys[7,15,16]. These policies aim to match donor and recipient ages more appropriately, addressing both the ethical considerations and practical outcomes of transplantation. According to the Korean Society of Nephrology (KSN) ESRD registry, by the end of 2019, the number of hemodialysis (HD) centers had exceeded 1,000, and there were more than 30,000 HD machines available[1]. The increased availability and improved management of dialysis have led to a reduction in the overall mortality rate among HD patients[1]. Consequently, there is a growing need to compare the outcomes of KT with those of patients on the waitlist undergoing dialysis, particularly focusing on elderly individuals with comorbidities who are at an elevated risk of complications following KT. The purpose of this study is to compare the patient survival rates of KT in elderly patients (aged over 60 years) with those of patients on the waiting list.

2. Materials and Methods

Patients

The present study is a retrospective and observational examination conducted at Asan Medical Center (AMC), analyzing a group of individuals aged 60 and older who received their first deceased donor kidney transplant between January 2008 and December 2022. The cohort included patients aged 60 and above and only first-time KT recipients were included in this study. Patients who underwent multiple KT (n=17), as well as those who received multiple organ transplants, including pancreas (n=16), heart (n=4), and liver (n=1) transplants, were excluded from the study. As a result, 165 participants were finally included in the KT group. For the comparative analysis, the waiting list group consisted of 895 patients who were registered on AMC's kidney transplantation (KT) waiting list during the study period. Approval for the research methodology was provided by the Institutional Review Board at AMC (AMC IRB 2023-0391). Given the study's retrospective nature and its classification as a Level 1 study with minimal risk, the IRB exempted it from the requirement for informed consent. Data collection for this research spanned from June 1, 2022, to September 28, 2023. The ethical standards followed in this study were in accordance with the principles stated in the World Medical Association Declaration of Helsinki.

Immunosuppression

Immunosuppressive treatment conformed to the established protocols of Asan Medical Center (AMC)[17]. The choice of induction therapy was based on immunological risk, employing either basiliximab, an anti-IL-2 receptor monoclonal antibody, or anti-thymocyte globulin (ATG). ATG was used in patients exhibiting high panel-reactive antibody (PRA) levels or donor-specific antibodies (DSA). Initial maintenance therapy incorporated a regimen of calcineurin inhibitors, corticosteroids, and mycophenolate mofetil. During the early postoperative period, the prescribed target trough levels for tacrolimus and cyclosporine were maintained at 7–10 ng/ml and 100–150 ng/mL, respectively. Cyclosporine was used in instances of tacrolimus intolerance or for those assessed as at high risk of infection. After the first postoperative year, these target concentrations for tacrolimus and cyclosporine were gradually lowered to 3–6 ng/mL and 50–100 ng/L, respectively. Steroid therapy was initiated with intraoperative methylprednisolone at a dose of 500mg, followed by gradual reduction, with most patients being maintained on approximately 4mg/day of methylon one year following KT.

Definitions

The time from transplantation to the recipient's death was defined as patient survival (PS) in transplant group. The PS of waiting list group, defined the time from registered to KT waiting list to the patients' death. To evaluate the risk factors for PS, we examined the history of cardiovascular disease (CVD) in patients. CVD is categorized into cardiac disease and CVA. Cardiac disease is defined as having a history of percutaneous coronary intervention (PCI), an ejection fraction (EF) of 50% or less as determined by echocardiography, or the presence of atrial fibrillation (AF) as indicated by electrocardiogram findings. CVA is defined as cases where patients exhibited acute infarction in MRI findings accompanied by neurological symptoms and had a medical record of a past history of symptomatic cerebral infarction. In the subgroup analysis, patients with cardiac disease and CVA were categorized as the CVD group Extended Criteria Donors (ECDs) are defined as donors aged 60 years or older, or those between 50 to 59 years with at least two of the following risk factors: a history of arterial hypertension, serum creatinine levels greater than 1.5 mg/dL, or a cause of death due to CVA[18]. The Kidney Donor Risk Index (KDRI) and the Kidney Donor Profile Index (KDPI) were utilized to assess the risk associated with donor kidney grafts[19].

Statistics

In our study's statistical analysis, categorical variables were analyzed using the Chi-squared test or Fisher's exact test as appropriate. For continuous variables, the Student's t-test was employed. Kaplan-Meier analysis was used to determine cumulative rates of postoperative stroke (PS), and differences between groups were evaluated using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify factors affecting PS, with results expressed as hazard ratios (HRs). Variables with a P-value of less than 0.1 in the univariate analysis were subsequently included in the multivariate model. Statistical computations were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Patient demographic and clinical characteristics

In this study, 1060 patients were analyzed, which included 165 (15.6%) KT recipients and 895 (84.4%) patients on the waiting list. The KT group had a significantly lower mean age (63.8 ± 3.4 years) compared to those on the waiting list (65.4 ± 4.4 years; $p<0.001$). Cardiac disease was observed in 11.1% of the total cohort, with significant

differences between the groups (p=0.029); this included a lower incidence of PCI, heart failure (EF <50%), and AF in the KT group compared to the waiting list group. The prevalence of CVA showed no significant difference between the two groups. In the KT group, 35.2% of patients had diabetes mellitus, and the mean duration of dialysis prior to transplantation was 95.1 ± 68.5 months. The mean panel reactive antibody (PRA) class I and II levels were 18.1 ± 27.6 and 15.1 ± 25.7, respectively, with an average HLA mismatch of 3.1 ± 1.9. Among the KT recipients, 91.5% were treated with tacrolimus, while 8.5% received cyclosporine. Induction therapy predominantly consisted of basiliximab (83.6%) and anti-thymocyte globulin (15.2%). Additionally, 53.9% of the transplants involved ECDs, with a mean KDPI of 72.3 ± 25.5 and a mean KDRI of 2.5 ± 13.8. (**Table 1**)

Table 1. Baseline and clinical characteristics

	Total	**KT**	**Waiting list**	***P*-value**
Number of patients	1060 (100)	165 (15.6)	895 (84.4)	-
Mean age (years)	65.1 ± 4.2	63.8 ± 3.4	65.4 ± 4.4	<0.001
Female sex	644 (60.8)	101 (61.2)	543 (60.7)	0.89
Cardiac disease				0.029
PCI	118 (11.1)	14 (8.5)	104 (11.6)	
Heart failure (EF <50%)	82 (7.7)	8 (4.8)	74 (8.3)	
Atrial fibrillation	107 (10.1)	10 (6.1)	97 (10.8)	
CVA	127 (12.0)	22(13.3)	105 (11.7)	0.56
Transplantation characteristics				
Diabetes mellitus		58 (35.2)		N/A
Dialysis duration		95.1 ± 68.5		N/A
PRA class I		18.1 ± 27.6		N/A
PRA class II		15.1 ± 25.7		N/A
HLA mismatch		3.1 ± 1.9		N/A
Calcineurin inhibitor				N/A

Tacrolimus	151 (91.5)	
Cyclosporin	14 (8.5)	
Induction		N/A
Basiliximab	138 (83.6)	
Anti-thymocyte globulin	25 (15.2)	
ECD donation	89 (53.9)	N/A
Donor KDPI	72.3 ± 25.5	N/A
Donor KDRI	2.5 ± 13.8	N/A

Continuous data are presented as means ± standard deviations. Categorical data are presented as a number (%)

Abbreviations: KT, kidney transplantation; PCI, percutaneous coronary intervention; EF, ejection fraction; CVA, cerebrovascular accident; PRA, panel reactive antibody; HLA, human leukocyte antigen; ECD, extended criteria donor; KDPI, kidney donor risk factor; KDRI, kidney donor risk index; N/A, not applicable

Overall patient survival

The Kaplan-Meier analysis of PS revealed no significant difference between the transplant and waiting list groups (p=0.76). When stratified by age, patients under 65 years showed no significant difference in PS between two groups (p=0.25). However, in patients aged 65 or above, there was a tendency for those on the waiting list to have better long-term graft survival, although this did not reach statistical significance (p=0.063). (**Figure 1**) When dividing the patient group based on age, either above or below 65 years, and the presence or absence of cardiovascular disease (CVD, in patients under 65 years of age, a trend toward better PS was observed among those without CVD who received a transplant, while a tendency toward poorer PS was seen in transplant recipients with CVD. However, long-term patient survival did not show a statistically significant difference between transplant recipients and those on the waiting list, regardless of the presence or absence of CVD (p=0.082). (**Figure 2A**) In patients over 65 years of age, there was no significant difference in PS between those who received a transplant and those on the waiting list among patients without CVD. However, in patients with CVD, those who remained on the waiting list showed significantly better long-term PS rates (p<0.001). (**Figure 2B**)

Figure 1. Overall patient survival rate: (A) in the entire study cohort, (B) in patients under 65 years, and (C) in patients aged 65 or above.

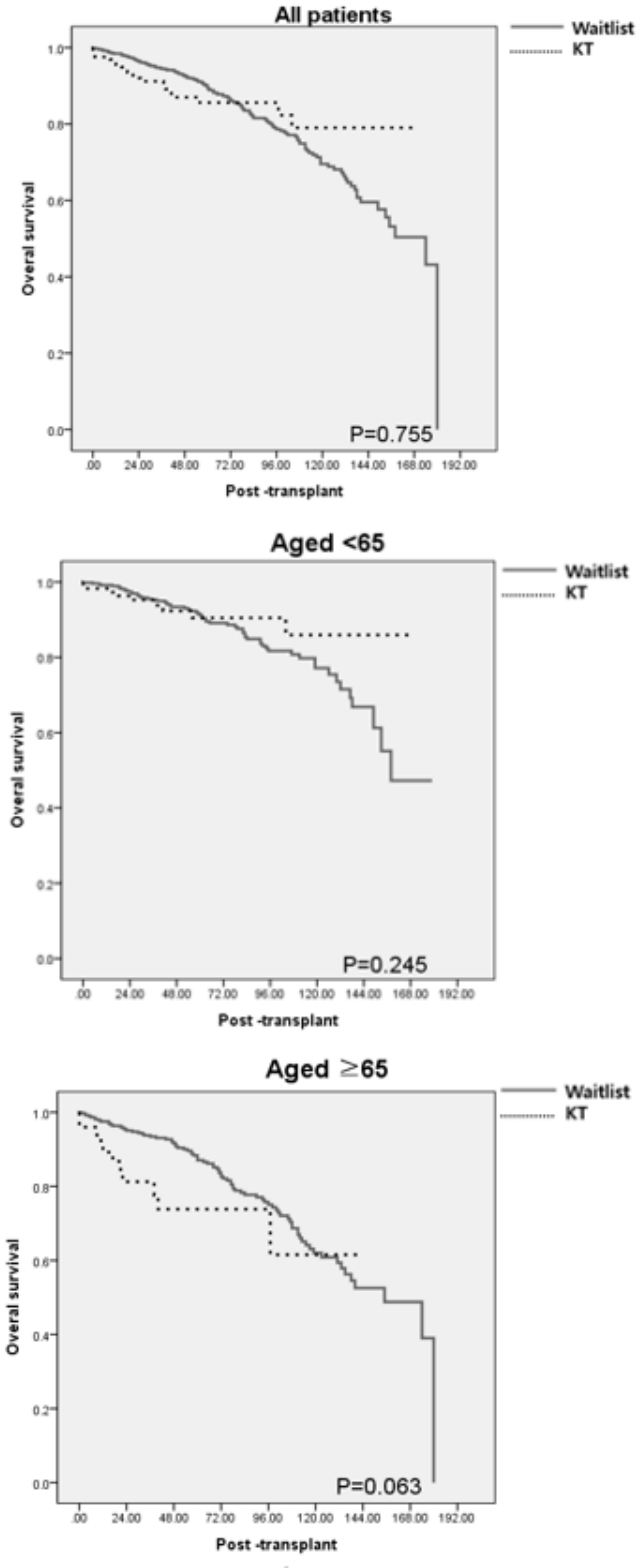
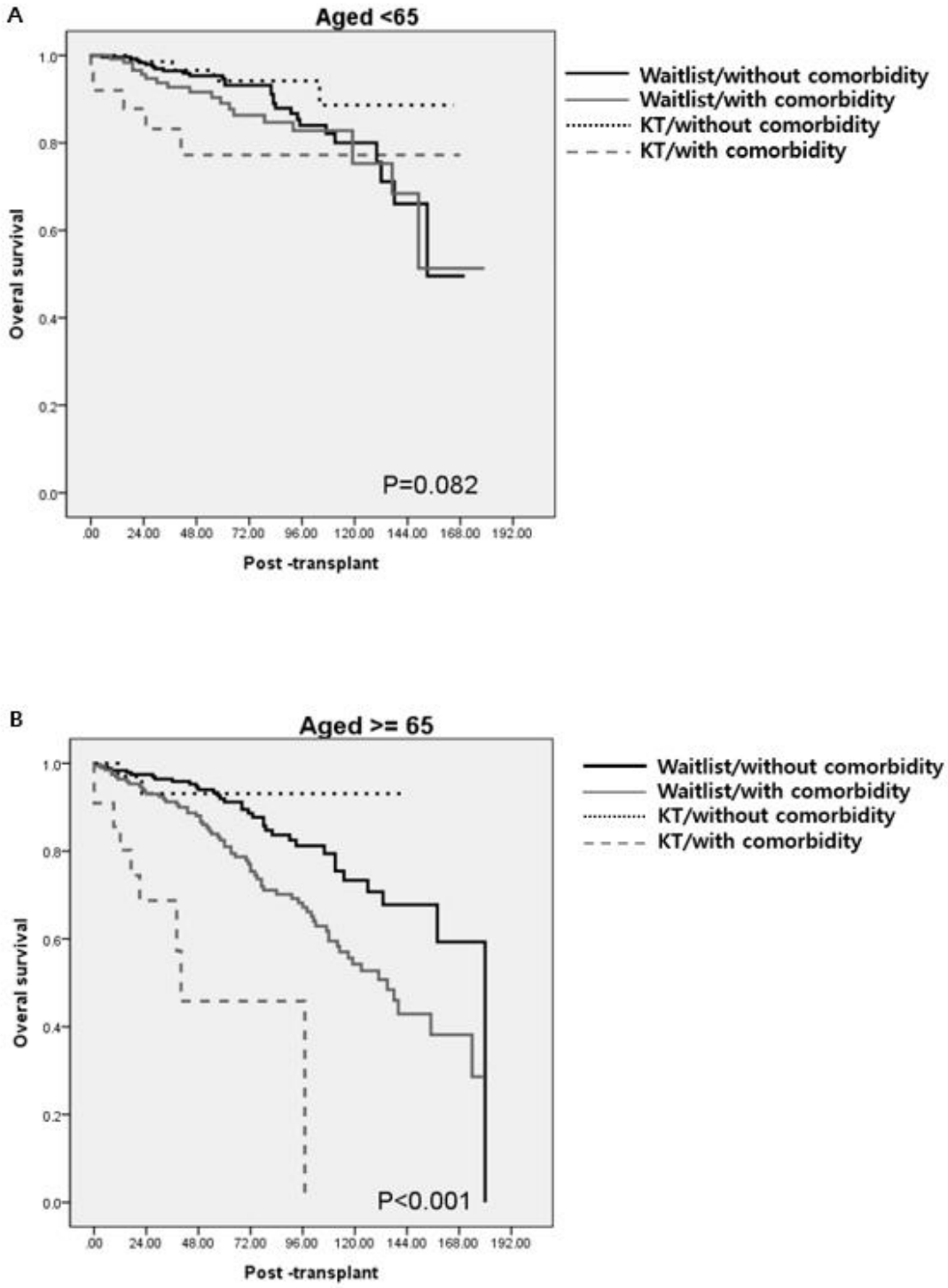


Figure 2. Overall patient survival rate stratified by age and presence of cardiovascular disease: (A) in patients under 65 years, and (B) in patients aged 65 or above



Risk factors associated with patient survival

In the univariate regression analysis, age, diabetes mellitus, cardiac disease, and CVA were identified as independent risk factors affecting PS. However, factors such as ECD, KDPI, and KDRI did not demonstrate a significant impact on PS. After adjusting for confounding variables, the multivariate analysis revealed that age (with a hazard ratio (HR) of 1.14, 95% CI: 1.01–1.29, p=0.038), diabetes mellitus (HR=3.35, 95% CI: 1.11–10.13, p=0.032), atrial fibrillation (HR 7.24, 95% CI: 2.16–24.34, p=0.001), and CVA (HR 6.49, 95% CI: 2.51–16.76, p<0.001) were statistically significant risk factors for PS. (**Table 2**)

Table 2. Risk factors for patient survival following deceased donor kidney transplant

	Univariate analysis		**Multivariate analysis**	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age	1.22 (1.10–1.36)	<0.001	1.14 (1.01–1.29)	0.038
Female sex	1.98 (0.72–5.45)	0.19		
PRA class I	0.99 (0.97–1.01)	0.21		
PRA class II	0.99 (0.97–1.01)	0.37		
Dialysis duration	1.00 (0.99–1.01)	0.93		
HLA mismatch	0.93 (0.74–1.16)	0.51		
Diabetes mellitus	2.89 (1.18–6.95)	0.021	3.35 (1.11–10.13)	0.032
Cardiac disease		0.001		0.028
PCI	1.72 (0.38–7.70)	0.48	3.57 (0.70–18.22)	0.13
Heart failure	1.43 (0.19–11.02)	0.73	1.31 (0.14–11.94)	0.81
Atrial fibrillation	8.42 (2.92–24.27)	<0.001	7.24 (2.16–24.34)	0.001
CVA	10.71 (4.39–26.13)	<0.001	6.49(2.51–16.76)	<0.001
ECD donation	1.10 (0.45–2.65)	0.84		
Donor KDPI	1.00 (0.99–1.02)	0.71		
Donor KDRI	0.99 (0.77–1.24)	0.84		

Abbreviations: PRA, panel reactive antibody; HLA, human leukocyte antigen; HLA, human leukocyte antigen; PCI, percutaneous coronary intervention; EF, ejection fraction; HF, heart failure; CVA, cerebrovascular accident; ECD, extended criteria donor; KDPI, kidney donor

risk factor; KDRI, kidney donor risk index

Causes of death in deceased donor kidney transplant patients

Table 3 showed the mortality and causes of death among 165 transplant patients. The total number of patients was 165, with 118 (71.5%) having no history of CVD and 47 (28.5%) with CVD. The overall mortality rate was 12.1%, being significantly higher in patients with CVD (29.8%) compared to those without CVD (5.1%). The leading cause of death was infection, affecting 13 patients (7.8% of the total cohort), with a higher prevalence in the CVD group (n=8, 17.0%) compared to the non-CVD group (n=5, 4.2%). Pneumonia was the most common infection, causing deaths in 11 patients (6.7%). Other infectious causes included enteritis (n=1, 0.6%) and cellulitis (n=1, 0.6%). Non-infectious causes were myocardial infarction (n=1, 0.6%), malignancy (n=2, 1.2%), and unknown cause (n=1, 0.6%).

Table 3. Causes of death in deceased donor kidney transplant patients

	Total	Without CVD	With CVD
Number of patients	165 (100)	118 (71.5)	47 (28.5)
Mortality	20 (12.1)	6 (5.1)	14 (29.8)
Cause			
Infection	13 (7.8)	5 (4.2)	8 (17.0)
Pneumonia	11 (6.7)	4 (3.4)	7 (14.9)
Enteritis	1 (0.6)		1 (2.1)
Cellulitis	1 (0.6)	1 (0.8)	
Myocardial infarction	1 (0.6)		1 (2.1)
Malignancy	2 (1.2)	1 (0.8)	1 (2.1)
Ischemic bowel disease	3 (1.8)		3 (6.4)
Unknown	1 (0.6)		1 (2.1)

Categorical data are presented as a number (%)

4. Discussion

This study suggested that in elderly patients, particularly those with CVD and other high-risk comorbidities, KT may not necessarily offer better survival compared to maintaining dialysis in the waiting list group. Especially as age increases, and in the presence of diabetes, atrial fibrillation, or CVA, kidney transplantation was found to potentially increase the risk of mortality. In patients aged 60 and above, these factors proved to be so influential that traditional risk factors for post-transplant survival, such as ECD, KDPI, and KDRI, as well as the duration of dialysis, did not yield significant results in the multivariate analysis. Although there are differences between studies due to varying characteristics of patient groups, ischemic times, and the status of donor kidneys, our study's five-year PS rate of 85% in the transplant group aligns with recently reported outcomes ranging from 65% to 85% in elderly patients[3,10,20-24]. Patients on the waiting list in our study appeared to exhibit a better PS rate of 89% compared to a recent study among elderly patients on the waiting list, which showed a PS rate of approximately 60%[23,25]. This phenomenon may be attributed to the exclusion of patients with severe health issues or significant comorbidities from the kidney transplantation registration process, making them ineligible for transplantation[26]. Additionally, during the process of preparing for transplantation and while waiting for a KT, pre-assessment and management of risk factors for mortality are carried out. As a result, the PS in the waiting list group could be overestimated when compared to the general dialysis population. In a prior study using U.S. data, patients on dialysis awaiting transplantation had a 38 to 58 percent lower standardized mortality ratio compared to all dialysis patients[13]. Therefore, it is essential to consider these factors when comparing the waiting list group to the transplant group in this study.

Generally, KT has been reported to provide long-term overall survival benefits, even in elderly patients[4,13,24]. In our study, we also observed a trend indicating that in the group without comorbidities, the KT group, regardless of age (under 65 or above), showed a tendency towards long-term survival benefits compared to the waiting list group. However, in elderly patients undergoing KT, factors such as patient age, comorbidities, dialysis duration, donor age, and graft condition may have a more pronounced impact on mortality, making them more vulnerable to these influences compared to younger patients[3,8,9,19,22]. As in previous studies, our cox proportional regression analysis also identified similar risk factors for PS, including age, diabetes mellitus, cardiac disease, and cerebrovascular accidents (CVA). However, other conventional risk factors for patient survival, such as ECD, KDPI, and KDRI scores, did not show significance, even in univariate analysis. This might be because most relatively young patients who waited long enough to

receive grafts from younger donors usually declined to receive kidneys that strayed from the standard criteria donor. Therefore, elderly patients tend to receive kidneys from ECD or older donors. In our study, elderly patients received kidneys with an ECD ratio of over 50%, KDPI scores of 72.3, and KDRI scores of 2.5, which were quite high. This suggests that one of the reasons for lower patient survival, especially in the CVD group among transplant recipients, may be the fact that relatively vulnerable elderly patients received kidneys that deviated from the standard criteria donor.

KT in elderly patients has also been reported to offer long-term survival benefits compared to being on the waiting list. This benefit is particularly pronounced when transplantation is preemptive and the KDPI score is low[24]. However, these studies compare outcomes for the entire study population and do not evaluate whether there is a benefit for personalized risk assessment compared to the waiting list. Recently, research on risk evaluation for tailored approaches for each individual has emerged. Chen et al. developed a scoring system in their study, where they scored factors associated with 5-year survival to divide patients into five risk groups. They reported significant differences in patient survival between the highest and lowest risk score groups, with a 47% five-year mortality for the lowest risk group and over 90% for the highest risk cohort[25]. Additionally, Bae et al. developed a tool based on the estimated post-transplant survival score and KDPI, allowing for the direct assessment of risk reduction and its extent between KT recipients and waiting list candidates, contributing to more individualized decision-making[14]. In particular, the survival rates of dialysis patients are significantly influenced by the healthcare systems in various countries and even within regions of the same country. Therefore, there is a need for the development of more specific risk assessment tools for dialysis and transplantation tailored to each healthcare environment. In South Korea, the widespread availability of community dialysis centers and the support of national health insurance for providing substantial financial support have led to significant improvements in the survival rates of dialysis patients, including elderly individuals with diabetes[1]. Given the current situation, it is essential to conduct in-depth research on the survival benefits for elderly high-risk patients undergoing transplantation, taking into consideration both patient survival and the efficient allocation of scarce donor organs.

Our study has several limitations. Firstly, it is a retrospective study conducted at a single center, which may not fully represent the entire population of transplant and dialysis patients. Secondly, in the comparison of long-term survival, the transplant group consisted of patients who had already spent some time on the waiting list before receiving a kidney transplant. This difference in the starting point ofaf survival comparison could potentially result in an underestimation of the survival rate in the elderly transplant group. Conversely,

the waiting list group may have been overestimated compared to both general dialysis patients and other waiting list groups. Thirdly, the patients in the waiting list group primarily received dialysis at local centers and did not undergo regular laboratory or physical examinations. Obtaining more detailed information for analyzing risk factors was challenging in this group.

5. Conclusion

Our study suggests a trend towards improved survival in elderly patients undergoing KT compared to those on the waiting list. However, it also highlights that in elderly patients, particularly those with comorbidities such as AF or CVA, KT may pose additional risks when compared to dialysis. Therefore, it is crucial for each transplant center to make efforts in developing tools for assessing their own transplant survival rates and the risk profiles of their local community's dialysis patients. These efforts can facilitate a more individualized and objective risk assessment, ultimately contributing to increased survival rates among elderly patients and the efficient allocation of scarce donor kidneys.

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국문요약

배경

기대 수명의 증가에 따라 고령의 신장 이식 환자와 이식 대기 목록에 등록된 투석 환자가 증가하고 있습니다. 본 연구는 고령 (60세 이상)의 신장 이식을 받은 환자와 대기 목록에 있는 환자들의 생존율을 비교하고자 합니다

연구방법

아산의료원에서 실시한 이 회고적 분석에는 2008년 1월부터 2022년 12월까지 처음 뇌사자 신장 이식을 받은 60세 이상의 환자가 포함되었습니다. 이식 환자 및 대기자의 특성과 신장 이식과 관련된 요소가 분석되었습니다.

결과

이식 및 대기 목록 그룹 간의 생존율 비교에서 이식 그룹에서 장기 생존율에 대해 유리한 경향이 나타났으나 통계적으로 유의미하지 않았습니다. 이어서 심혈관 및 뇌혈관 질환의 존재 여부 및 연령(65세 이전 및 이후)을 기준으로 한 추가 분류가 이루어졌습니다. 이식 그룹에서 65세 미만의 환자 중 동반 질환 없는 군은 생존율에 유리한 경향이 나타났습니다. 65세 이상이고 동반 질환 없이 이식을 받은 환자들은 통계적으로 유의미하지 않았지만 장기 생존율에 유리한 경향이 나타났습니다. 그러나 동반 질환 있는 이식 그룹은 대기 목록 그룹과 비교했을 때 불리한 생존율을 보여주었습니다.

결론

본 연구는 고령의 신장 이식 그룹이 대기 그룹보다 생존율에서 유리한 경향을 나타냅니다. 그러나 동반 질환을 가진 고령 환자에서는 투석보다 이식이 더 큰 위험을 가질 수 있습니다. 따라서 이식 센터는 자체적으로 등록된 환자들의 생존율과 투석 환자들의 위험도를 평가하기 위한 도구를 개발해야 합니다. 이러한 노력은 고령의 말기신부전 환자의 생존율을 향상시키고 신장 기증 공급이 제한되고 있는 상황에서 신장 기증의 효과적인 할당을 위해 중요합니다.