Analysis of Clinical Outcomes According to the Definition of Slow Graft Function in Deceased Donor Kidney Transplantation

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ABSTRACT

Background. Slow graft function (SGF) is considered to be an intermediate state between immediate graft function (IGF) and delayed graft function (DGF). However, the criteria of SGF is still arbitrary, and the clinical outcomes of SGF are not fully understood.

Methods. A total of 212 deceased donor kidney transplantation recipients were enrolled. Three schemas were adopted, which classified SGF according to the serum creatinine (Cr) level by a given postoperative day (POD). SGF was defined as Cr $\geq$ 3.0 mg/dL on POD5, Cr $\geq$ 2.5 mg/dL on POD7, and Cr $\geq$ 1.5 mg/dL on POD14 without dialysis in schema I, II, and III, respectively. Estimated glomerular filtration rate (eGFR) after transplantation, acute rejection, and graft survival were compared in each schema. Decreased renal function, defined as eGFR less than 30.0 mL/min/1.73m^2, was also compared.

Results. In schema I and III, SGF had significantly lower eGFR at 3 months after transplantation compared with IGF ($P < .017$), and only schema III maintained the difference until 36 months after transplantation. The incidence of decreased renal function showed significant difference among groups in schema I and III ($P < .05$). Graft survival did not show significant difference among groups in all schemas. However, SGF and DGF groups showed a higher probability of decreased renal function than the IGF group ($P < .017$) in schema I and III.

Conclusions. In deceased donor kidney transplantation, certain definitions of SGF identified significantly worse clinical outcomes compared with IGF, suggesting similar impact with DGF. It is necessary to reach a consensus on a clearer definition of SGF with further studies.

ALTHOUGH kidney transplantation (KT) is considered a good treatment choice for patients with end-stage kidney disease [1,2], it is difficult for patients on the waiting lists to have an opportunity for transplantation [3]. Even after transplantation, patients sometimes confront poor clinical outcomes with reduced graft function in deceased donor KT (DDKT) [4]. Reduced graft function, especially in the early stage of KT, is associated with subsequent graft outcomes and survival rates [5,6].

Graft function in the immediate postoperative period is generally focused on whether or not the patient is having delayed graft function (DGF), which requires dialysis within the first week after transplantation [7]. DGF is known to be associated with poor clinical outcomes, such as increased acute rejection, prolonged hospital stay, and poor long-term

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graft survival rates [8,9]. However, even having a certain level of allograft function may avoid post-transplant dialysis, and there may be a condition that is different from immediate graft function (IGF), which shows good results from the early stage after transplantation. This group of allograft function has been defined as slow graft function (SGF), which was associated with a not rapidly falling serum creatinine (Cr) level post transplant but with a sufficient kidney function to avoid dialysis [10].

Unfortunately, studies about SGF have not received as much attention as DGF, and some limitations are identified with the previous studies. First, there is no consensus about the definition of SGF. SGF was generally considered a condition that did not require dialysis but had a slower decline of serum Cr level than IGF. Its specific criteria differs from study to study. It has been based on the absolute Cr level at a given postoperative day (POD) or inadequate Cr reduction ratio over a given period. Second, the clinical outcomes with SGF is not fully investigated, therefore its clinical impact on post-transplant outcome still remained controversial. In studies by Humar et al [10,11], SGF showed significantly higher incidence of early acute rejection and poor graft survival compared with IGF. Zeraati et al [12] identified that SGF showed significantly better graft survival than DGF, but the impact of SGF on graft survival was similar to IGF. Lee et al [13] revealed that SGF showed higher Cr level compared with IGF, and it affected the function and survival of the graft in the long-term period.

Therefore, the purpose of this study was to classify transplant recipients according to the definition of SGF and then to identify the distribution and clinical outcomes with SGF compared with IGF and DGF by each schema.

MATERIALS AND METHODS

This retrospective study was conducted at a single transplant center in the Republic of Korea. From January 2004 to June 2015, a total of 214 patients received DDKT at Kyungpook National University Hospital, Daegu, in Korea. Among them, 2 recipients with missing follow-ups at the early postoperative period were excluded. Therefore, a total of 212 DDKT recipients were included in the final analysis. All of the data was drawn from the electronic medical records at this single center.

In this study, 3 schemas defining SGF were adopted to compare the difference among groups. Each schema was drawn from previous studies, which defined SGF by its absolute Cr level at a given day. Not requiring dialysis in the first week after transplant is common to all 3 schemas; however, the 3 schemas were distinguished according to the Cr level at a given day. Cr $\geq$ 3.0 mg/dL on POD5 [10], Cr $\geq$ 2.5 mg/dL on POD7 [12], and Cr $\geq$ 1.5 mg/dL on POD14 [13] were defined as schema I, II, and III, respectively. For this study, if there was a need for dialysis in the first week post transplant, it was defined as DGF, while immediate excellent graft function was defined as IGF.

Transplant outcomes included not only acute rejection and irreversible graft loss but also estimated glomerular filtration rate (eGFR) up to 36 months after transplantation, which was calculated by the modification of diet in renal disease study (MDRD) equation. Decreased renal function, which is defined as an eGFR of less than 30.0 mL/min/1.73m^2, was also compared among groups in each schema. Differences in graft survival with irreversible graft loss and decreased renal function were also analyzed in each schema.

Statistical Analysis

Demographic characteristics were presented as the mean and standard deviation. Frequency and percentage were also used. To compare the difference among groups in each schema, analysis of variance, Kruskal-Wallis test, and post hoc test with Bonferroni method of correction were used. Nominal data was analyzed with χ^2 test, and Kaplan-Meier analysis was also used to compare graft survival among groups. Analysis was performed using SPSS (version 20.0, SPSS Inc, Chicago, IL, United States). A P value less than .05 was considered statistically significant, while a significant level of .017 ($P < .05/3$) was applied in the post hoc test to reduce the risk of type I errors.

RESULTS

Characteristics of the Enrolled Patients

The baseline demographic and clinical data of the 212 patients and their deceased donors are presented in Table 1. In terms of recipients, 56.6% were men, and the mean age was 46.3 years. Glomerulonephritis (67.9%) was the most common cause of primary kidney disease, followed by diabetes (20.3%) and hypertension (7.1%). For renal replacement therapy before KT, most (70.3%) recipients had

Table 1. Characteristics of the Enrolled Kidney Transplantation Patients (n = 212)

Variable	Mean ± SD (%)
Recipient	
Age (y)	46.3 ± 11.5
Sex	
Male	120 (56.6)
Female	92 (43.4)
Primary kidney disease	
Glomerulonephritis	144 (67.9)
Hyertension	15 (7.1)
Diabetic nephropathy	43 (20.3)
Polycystic kidney disease	5 (2.4)
Others	5 (2.4)
Dialysis type	
HD	149 (70.3)
PD	56 (26.4)
HD + PD	7 (3.3)
Donor	
Age y	43.3 ± 16.3
Sex	
Male	144 (67.9)
Female	68 (32.1)
Donor type	
SCD	175 (82.5)
ECD	37 (17.5)

Data are given as frequency and percentage or mean and standard deviation, as appropriate.

Abbreviations: ECD, expanded criteria donor; HD, hemodialysis; PD, peritoneal dialysis; SCD, standard criteria donor; SD, standard deviation.

Table 2. Distribution of Graft Functions After Kidney Transplantation by Different Schemas

	Schema I				Schema II				Schema III			
	IGF	SGF	DGF	*P*	IGF	SGF	DGF	*P*	IGF	SGF	DGF	*P*
SCD (%)	146 (83.4)	15 (8.6)	14 (8.0)	.035	148 (84.6)	13 (7.4)	14 (8.0)	.259	130 (74.3)	31 (17.7)	14 (8.0)	<.001
ECD (%)	24 (64.9)	7 (18.9)	6 (16.2)		28 (75.7)	3 (8.1)	6 (16.2)		12 (32.4)	19 (51.4)	6 (16.2)	
Total	170	22	20		176	16	20		142	50	20	
(%)	(80.2)	(10.4)	(9.4)		(83.1)	(7.5)	(9.4)		(67.0)	(23.6)	(9.4)	

Data are given as frequency and percentage.
Abbreviations: DGF, delayed graft function; ECD, expanded criteria donor; IGF, immediate graft function; SCD, standard criteria donor; SGF, slow graft function.

hemodialysis, 26.4% had peritoneal dialysis, and 3.3% had combined therapy for hemodialysis and peritoneal dialysis. In terms of deceased donors, the mean age was 43.3 years old, and 67.9% were men. When classified based on the characteristics of deceased donor type, there were more standard criteria donors (SCD) (82.5%) than expanded criteria donors (ECD) (17.5%).

Distribution of SGF by Each Schema

The incidence of SGF showed different distribution by each schema. The number of patients with SGF were 22 (10.4%), 16 (7.5%), and 50 (23.6%) for schema I, II, and III, respectively. When comparing the distribution of SGF according to the deceased donor type, ECD showed higher percentage of SGF than SCD in schema I and III (18.9% vs 8.6%, $P = .035$ in schema I; 51.4% vs 17.7%, $P < .001$ in schema III) (Table 2).

Comparisons of Post-transplant Outcomes

In the comparison of eGFR among the 3 groups, there were significant differences in eGFR until 36 months after KT in all 3 schemas ($P < .05$, Fig 1). The post hoc test showed that SGF had significantly lower eGFR at 3 months after KT compared with IGF ($P < .017$) in schema I and III. The difference maintained until 36 months after KT only with schema III. There was no significant difference in eGFR between SGF and DGF until 36 months after KT in all 3 schemas (Table 3).

No significant differences were found in the incidence of acute rejection and irreversible graft loss among groups in all 3 schemas. However, the incidence of decreased renal function showed significant difference among groups in schema I and III ($P < .05$, Table 4). While graft survival with irreversible graft loss was not different among groups in all 3 schemas (data not shown), decreased renal function showed significant difference among groups in schema I and III ($P < .05$): SGF and DGF groups showed a higher probability of decreased renal function than IGF group ($P < .017$) in schema I and III (Fig 2). It took a mean of 18.8 ± 15.0 (range, 0–64) months from eGFR less than 30.0 mL/min/1.73 m^2 to irreversible graft loss.

DISCUSSION

Reduced graft function in the early period after KT might include not only conditions that require dialysis but also a slow decrease in post-transplant Cr without necessitating dialysis. The former is commonly referred to as DGF and is accepted as the traditional definition of DGF. A number of studies on early graft function after transplantation have focused primarily on the presence of DGF. They have shown that DGF had a detrimental effect on post-transplant outcomes [8,9]. However, the absence of DGF does not guarantee that graft function is as good as IGF, and this intermediate state might be more prevalent than DGF, especially in DDKT. Unlike the general agreement on the definition of DGF, many researchers adopted their own criteria of SGF in their studies. This suggests that there is a

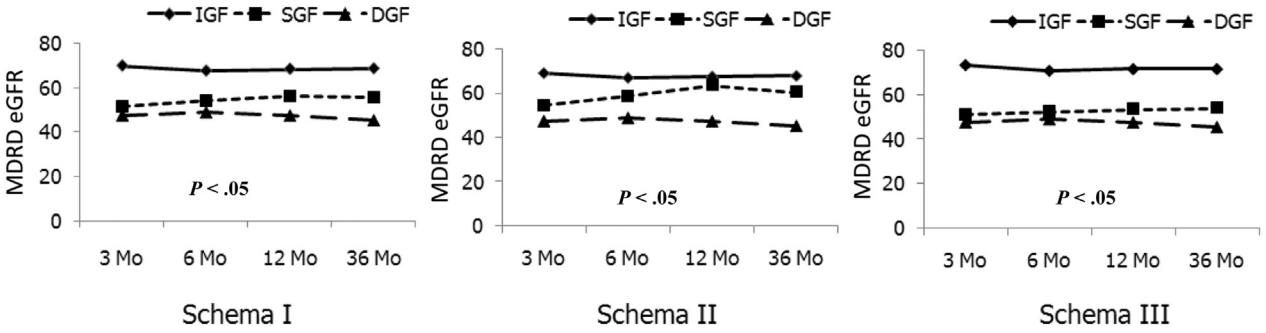

Fig 1. Comparisons of MDRD eGFR among 3 types of graft function by each schema. DGF, delayed graft function; eGFR, estimated glomerular filtration rate; IGF, immediate graft function; MDRD, modification of diet in renal disease study; SGF, slow graft function.

lack of consensus on the definition of SGF, which may lead to confusion in analyzing studies about SGF.

In this retrospective study, we explored the distribution of graft function in the immediate postoperative period and its clinical outcomes. The intermediate early graft function between IGF and DGF was defined as SGF in the study. Three schemas separated by the definition of SGF were adopted. Within each schema, kidney transplant recipients were divided into 3 groups according to their immediate graft function after KT.

When classified by the definition of SGF, the distribution of SGF was greater than DGF with schema I and III (10.4% and 23.6%, respectively). It is notable that the distribution of SGF was very large in schema III; this may be because schema III adopted a relatively long time point of 14 days after KT and a relatively tight Cr criteria of 1.5 mg/dL. In the previous studies, the incidence of DGF after DDKT varied according to the study ranging from 25% to 70% [14–16]. However the incidence of SGF has not been reported in detail, and there are few data about its incidence according to the deceased donor type. We compared the distribution of SGF according to donor type and showed that the immediate graft function might be different dependent on the type of deceased donor in schema I and III. Even though the donor was a SCD, the distribution of SGF was similar to or greater than DGF and was much greater than IGF when the donor was an ECD with a certain definition of SGF. This suggests that even if the donor is a SCD, SGF could develop after DDKT, and in case of ECD, much more attention should be paid to the occurrence of SGF.

In the analysis of the impact of SGF on acute rejection and graft survival, the results were not in accordance with each other. In a study by Rodrigo et al [17], acute rejection rates showed no significant difference between SGF and DGF, and IGF showed different values from both SGF and DGF. Johnston et al [18] reported that the acute rejection rate was significantly higher in DGF than both IGF and SGF. Humar et al [11] presented that IGF had significantly better graft survival than SGF, and SGF had better values than DGF, and Zeraati et al [12] found that graft survival was worse in DGF than SGF or IGF. Our study suggests that SGF was not associated with higher rate of acute rejection and worse graft survivals with irreversible graft loss compared with IGF or DGF in all 3 schemas.

When the graft outcome with eGFR was analyzed, SGF showed higher eGFR level than DGF; however, it was not significantly different in all 3 schemas. SGF displayed worse outcomes than IGF in schema I and III, and the difference continued until 36 months after transplantation in schema III. It suggests that if proper criteria of SGF were applied, SGF would predict the eGFR within a certain period after KT. To prove the ability of SGF to discriminate the graft function long-term post transplant,

Table 3. Comparisons of MDRD eGFR Among Groups by Each Schema.

	Schema I			Schema II			Schema III		
	IGF vs SGF	IGF vs DGF	SGF vs DGF	IGF vs SGF	IGF vs DGF	SGF vs DGF	IGF vs SGF	IGF vs DGF	SGF vs DGF
3 mo	.001*	<.001*	.488	.038	<.001*	.289	<.001*	<.001*	.363
6 mo	.029	.001*	.424	.440	.001*	.205	<.001*	<.001*	.635
12 mo	.073	.001*	.347	.742	.002*	.075	<.001*	<.001*	.574
36 mo	.079	.001*	.464	.587	.002*	.239	<.001*	<.001*	.453

Abbreviations: DGF, delayed graft function; eGFR, estimated glomerular filtration rate; IGF, immediate graft function; MDRD, modification of diet in renal disease study; SGF, slow graft function.

*The threshold significance was 0.05/3 = 0.017.

Table 4. The Incidences of Acute Rejection, Irreversible Graft Loss, and Decreased Renal Function Among Groups by Each Schema

	Schema I	Schema II	Schema III
Acute rejection			
IGF	12 (7.1)	12 (6.8)	7 (4.9)
SGF	9 (0.0)	0 (0.0)	5 (10.0)
DGF	2 (10.0)	2 (10.0)	2 (10.0)
P	.381	.544	.298
Irreversible graft loss			
IGF	20 (11.8)	22 (12.5)	18 (12.7)
SGF	5 (22.7)	3 (18.8)	7 (14.0)
DGF	4 (20.0)	4 (20.0)	4 (20.0)
P	.214	.438	.698
Decreased renal function			
IGF	25 (14.7)	29 (16.5)	20 (14.1)
SGF	9 (40.9)	5 (31.2)	14 (28.0)
DGF	6 (30.0)	6 (30.0)	6 (30.0)
P	.005*	.134	.039*

Data are given as frequency (percentage).
Abbreviations: DGF, delayed graft function; IGF, immediate graft function; SGF, slow graft function.
*The threshold significance was .05.

graft function must be followed up in patients with SGF for a longer period.

Out study analyzed graft outcome with the concept of decreased renal function, which defined as eGFR less than 30.0 mL/min/1.73 m^2. Graft survival with decreased renal function showed that SGF was worse than IGF and similar with DGF in schema I and III. Although there was a difference in duration from decreased renal function to irreversible graft loss, ranging from less than a month to over 5 years, if eGFR begins to fall below 30.0 mL/min/1.73 m^2, irreversible loss of graft function may initiate and may be related with frequent hospitalization or complete graft loss in the near future.

This study has some limitations. It was conducted in a single center with small sample size, and factors that might influence the clinical outcomes were not actively considered. However, as far as we know, this study was the first Asian study to compare different definitions of SGF and identify their clinical outcomes. In addition, by analyzing the clinical outcomes with the concept of decreased renal function, it presents a different view of graft survival from the previous studies.

Although the definition of SGF showed somewhat different results, certain definitions of SGF could predict significantly worse outcomes compared with IGF and had similar impact as DGF on transplant outcomes. Our study suggests that the definition of SGF needs to be clarified to estimate renal function after KT. Considering the relatively poor clinical outcomes of patients with SGF compared with IGF, it might lead to both physical and psychological problems subsequently. Therefore, multidimensional studies of SGF, which could cover both clinical and psychological aspects, are needed and should be pursued with as much interest as studies of DGF.

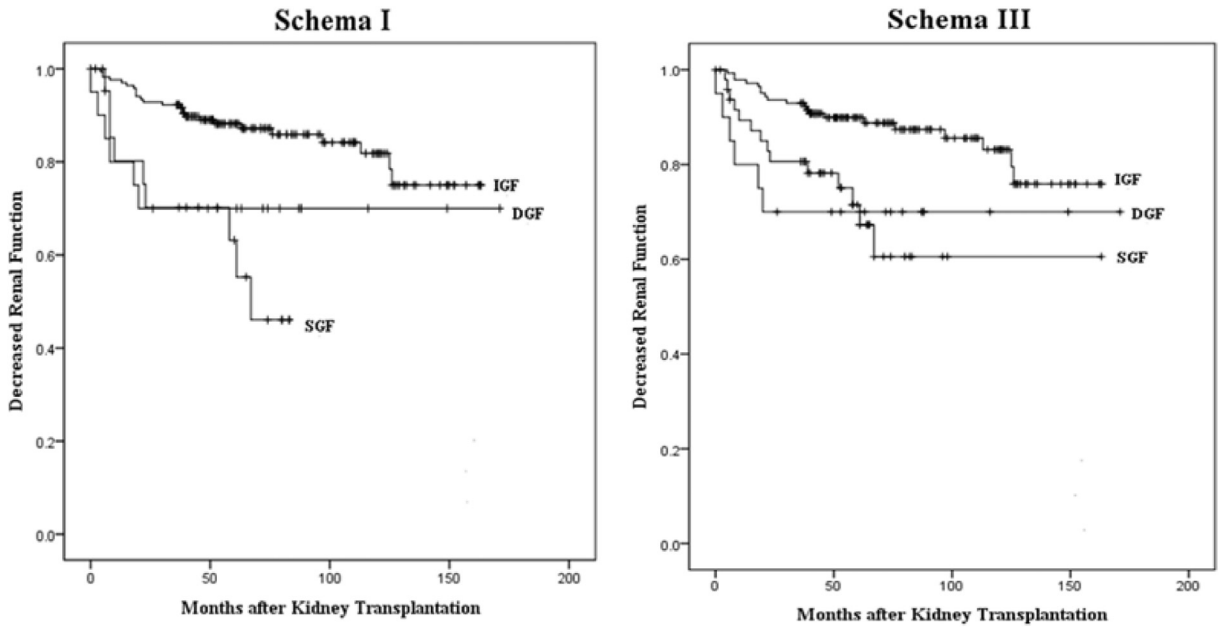

Fig 2. Kaplan-Meier analysis of decreased renal function less than 30 mL/min/1.73 m^2. DGF, delayed graft function; IGF, immediate graft function; SGF, slow graft function.

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