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Delayed graft function after a first isolated non-preemptive pediatric kidney transplantation in the French 2008-2018 cohort

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Abstract

Background and hypothesis

The aim of the study was to describe frequency, causes, and consequences of delayed graft function (DGF) on graft survival, in a comprehensive, multicenter French pediatric cohort.

Methods

DGF was defined as the need for dialysis within the first week after transplantation. After exclusion of primary non-function, all first isolated, non-preemptive kidney transplantation performed in the French pediatric transplant centers between January 2008 and December 2018 were included.

Results

Among the 612 patients included, DGF was observed in 60 (9.8%). Median DGF duration was 5.5 [IQR 3.0;9.3] days. Recipient age at transplantation was 12 [6;15] years and dialysis duration pre-transplantation 13.8 [7.0;24.0] months. Donors were brain-dead donors in 531 (86.8%) of cases. Deceased and living donor ages were 15 [10;17] and 40 [35;45] years, respectively. Cold (CIT) and warm (WIT) ischemia times were 14.5 [11.3;17.7] hours and 45 [35;61] minutes, respectively. After a median follow-up of 7.0 [4.9;10.2] years, 18 (2.9%) patients died and 90 (14.7%) lost their graft. Multivariable analysis found an association between DGF occurrence and both CIT (OR 1.07 95%CI 1.01–1.13), and WIT (OR 1.01 95%CI 1.00-1.02). There was no association between DGF and graft survival but longer DGF duration was associated with a decreased graft survival.

Conclusion

Longer cold and warm ischemia times are risk factors for DGF in pediatric kidney transplantation. No significant effect of DGF on graft survival was found in our cohort but DGF duration was overall short and was associated with reduced graft survival among recipients with DGF.

Introduction

Remarkable progress has been made in recent decades in the field of pediatric kidney transplantation (Tx), resulting in better patient and graft survival [1], preservation of the cardiovascular system [2], better growth [3], and improvement in patients' quality of life [4] compared with continued dialysis. It is therefore the gold standard treatment for patients with kidney failure. Delayed graft function (DGF), defined as the need for dialysis within the first week after Tx regardless of the cause [5], is associated in adults with more frequent acute cellular rejection and reduced short- and long-term graft survival [6, 7]. Long term outcome has been associated in adults with DGF duration [8]. In children, the reported

consequences of DGF are variable according to studies: no significant decrease of graft survival [9, 10], significantly lower graft survival after living [11] and deceased [12–14] donation, particularly in children < 10 years of age [12], and higher acute rejection rate after living donor Tx [11]. The median [interquartile range (IQR)] duration of DGF was 8 [14] days in one pediatric cohort from Australia and New Zealand Dialysis and Transplant (ANZDATA) registry [13].

The frequency of DGF is variable across pediatric studies, that differ based on the country where they are conducted, the period considered, and the inclusion or not of primary non-function (PNF) and pre-emptive Tx. For instance, in the United Network for Organ Sharing (UNOS) database, the most recent data from 2000 to 2020 report a frequency of 4.2% after living donor kidney Tx, PNF included [11], and 8.4% in the whole non-preemptive Tx cohort, PNF included [15]. This frequency was higher in the older (1994–2017) UNOS dead brain donor cohort: 10.6% [16]. A 5% decrease in odds of DGF with each more recent year of Tx was reported between 1987 and 2012 in the Scientific Registry of Transplant Recipients (SRTR) [17]. Kidney allocation rules can modify this frequency [12, 18], thus the frequency of DGF was 11.1% in non-preemptive deceased donor Tx performed between 2014 and 2016 in the SRTR cohort, after exclusion of PNF [18]. In the ANZDATA registry, DGF was reported in 22.3% of recipients transplanted with deceased donor (between 1990 and 2012 and donation after cardiac death included), this frequency decreased to 19.1% after exclusion of PNF [13]. In the United Kingdom from 2000 to 2014, DGF was reported in 10% of Tx from brain-dead donors after exclusion of PNF [19]. In the Cooperative European Paediatric Renal Transplant Initiative (CERTAIN) registry, DGF was reported in 11.8% of recipients transplanted with deceased donor and 1.8% of recipients transplanted with living donors (first and subsequent Tx, preemptive or post-dialysis, between 1997 and 2022) [20].

Many risk factors have been associated with DGF [8, 21, 22], among them prolonged cold (CIT) [20, 21, 23–28] and warm (WIT) [27, 29] ischemia times, and their combination [30], are key. Conversely, post-transplant intravenous fluid therapy with balanced crystalloid solution compared with saline [31] is a protective factor. In children, donation after cardiac death [13, 16, 19, 20, 32], older donor age [10, 13, 28], male donors [28], longer CIT [20, 28] and duration of dialysis pre-Tx are reported risk factors for DGF [9, 12]. Living donation has been reported to both be protective [19, 20, 33] and not [15], and preemptive Tx has been reported as protective [9, 20], but this association was not retrieved in a systematic review and metanalysis [34].

The aim of the present study was to determine, in a comprehensive, multicenter French pediatric cohort, the frequency and duration of DGF, the risk factors associated with its occurrence, and the association of DGF with graft survival.

Material and methods

Data collection

The French *Agence de la Biomédecine* is a public institution supported by the French ministry of health. One of its missions is to manage organ and tissue procurement as well as Tx in France. For this purpose, the French national transplant registry (Cristal) prospectively collects demographic, clinical, and laboratory data for all Tx recipients and donors in France, as well as Tx outcomes. Data are recorded at registration (placement on a Tx waiting list), procurement, Tx, and annually thereafter. Data collection is mandatory, and clinical research associates double-check its completeness and accuracy. In compliance with French law, studies based on this national registry are part of transplant assessment and do not require additional institutional review board approval. The database has been reported to the national data protection agency (*Commission nationale de l'informatique et des libertés*). For the present study anonymized data were retrieved from the Cristal registry on May 17, 2023.

Study population and variables

All children up to 18 years of age who received a first isolated, non-preemptive kidney transplant in the 14 French pediatric kidney transplant centers between January 1, 2008 and December 31, 2018 were included. Patients with PNF were excluded.

Donor variables considered in the study were: age, sex, height, living or deceased donor status, cause of deceased donor death, donor serum creatinine and estimated glomerular filtration rate (eGFR; calculated using the European Kidney Function Consortium [EKFC] equation) [35], human leukocyte antigen (HLA) typing, Cytomegalovirus (CMV) and Ebstein-Barr virus (EBV) status. Recipient variables considered were: age, sex, weight, height, cause of kidney failure, duration of pre-transplant dialysis, waiting time on the list, HLA typing, CMV status, DGF occurrence and duration, as well as graft and patient survival during follow-up

Transplant-related variables considered in the study were: side of transplanted kidney, CIT (defined as the duration of cold storage), WIT (defined as the time between organ removal from cold storage and allograft reperfusion), and transplant centers.

Statistical analysis:

Data are expressed as mean ± standard deviation (SD) or median [IQR] (according to the distribution of the variable), count (percentage), odds ratio (OR), hazard ratio (HR), and 95% confidence interval (95%CI). Once the various parameters had been collected, patients were divided into two groups according to whether or not they had experienced a DGF. The distributions of baseline variables were compared across groups using the Chi-squared or Fisher's exact tests for categorical measures, and the Kruskal-Wallis test for continuous variables.

We adjusted univariable and multivariable logistic regression models to assess factors associated with the occurrence of DGF. The following factors were considered in the analysis: ischemia times, type of donor (living or deceased), donor and recipient sex and age, donor eGFR, pre-Tx dialysis duration, and

transplant center. The final multivariable model, selected on the basis of the lowest Akaike Information Criterion (AIC) using a stepwise approach with both forward selection and backward elimination, is presented. To avoid including redundant information and ensure interpretability, models including either donor and recipient age, or their age ratio, were compared using AIC. For the transplant center, which has many levels, only the overall Analysis of Deviance Table p-value is shown. Age and height ratios were highly correlated between recipients and donors. The addition of either did not seem to affect the effect of the other parameters. Since there were more missing data for the height ratio, the age ratio was used in the different models herein. Shorter WIT in one center led us to compare *post-hoc* the center DGF rates to all the other centers using the univariable regression model previously described. WIT times were compared between this center and the other centers using the Wilcoxon rank-sum test. After showing the association between recipient/donor age ratio and DGF, a second *post-hoc* analysis consisted in dichotomizing the age ratio in older/same age of recipient compared to donor or younger recipient compared to donor.

Graft survival, stratified by DGF status, was estimated using the Kaplan-Meier method. The association between DGF and graft survival was analyzed using Cox proportional hazard models including following covariates: DGF, donor type (deceased or living), donor age, recipient age, recipient/donor age ratio, pre-transplantation dialysis duration, transplant center, side of donor kidney, CIT and WIT, number of HLA mismatches, and idiopathic nephrotic syndrome as primary disease. The final multivariable model, selected on the basis of the lowest AIC using a stepwise approach with both forward selection and backward elimination, is presented while DGF was included in all models by design. For these survival models, patients were censored at date of last follow-up or death. The association between the duration of DGF and graft survival was analyzed in the 60 patients with DGF using Cox proportional hazards models that included the same covariates, but with DGF replaced by the duration of DGF.

For all tests statistical significance was considered when p-value < 0.05. All statistical tests were performed using R version 4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among 868 children who received a first isolated kidney Tx during the study period; 256 were excluded, 32 of whom had PNF (Fig. 1) that was reported among 659 (4.9%) patients with first isolated non-preemptive Tx. Patients with PNF did not differ significantly from included patients in terms of primary disease (suppl Table 1), recipient characteristics, as well as waiting and ischemia times (suppl Table 2), but deceased donors were younger (p = 0.027) with notably more donors ≤ 5 years old (suppl Table 3), and cause of graft loss was significantly different (p < 0.001) with notably a greater frequency of graft loss due to thrombosis: 78.1% (25/32) among those with PNF group than among those without PNF (0%; suppl Table 2).

Description of recipients, donors, and transplantations

Among the 612 children with non-preemptive first kidney Tx included, 531 (86.8%) received a kidney from a brain-dead deceased donor. The median [IQR] recipient age at the time of Tx was 12 [6;15] years. The pre-Tx dialysis duration was 13.8 [7.0;24.0] months, the waiting time on the list before Tx was 7.8 [3.8;14.6] months (Table 1). CIT was 14.5 [11.3;17.7] hours, and WIT 45 [35;61] minutes. Median post-transplant follow-up was 7.0 [4.9;10.2] years (Table 2). The distribution of primary disease according to the occurrence or not of DGF was not significantly different (suppl Table 4). Donor age was 16 [12;20] years, donor eGFR was 101 [72;113] ml/min/1.73m², donor/recipient age difference was 4 [-1;11] years, and 25.7% of donors were younger than their recipient (Table 3). DGF was observed in 60 (9.8%) recipients. DGF duration was 5.5 [3.0;9.3] days, with 54 (90%) of DGF lasting ≤ 14 days and 6 (10%) between 15 and 79 days.

Table 1
Recipients' characteristics, waiting time and pre-transplantation dialysis duration

Recipient age, years	**Patients with available data, n (%)**	**Total population**	**Patients with DGF**	**Patients without DGF**	**p**
Total population, n (%)	612 (100)	612 (100)	60 (9.8)	552 (90.2)	
median [IQR]		12 [6;15]	14 [8;15]	12 [6;15]	0.042
≤ 2, n (%)		26 (4.2)	3 (5.0)	23 (4.2)	0.258
]2-≤5, n (%)		115 (18.8)	8 (13.3)	107 (19.4)	
]5-≤10, n (%)		132 (21.6)	9 (15.0)	123 (22.3)	
]10-≤18, n (%)		339 (55.4)	40 (66.7)	299 (54.2)	
Deceased donor Tx, n (%)	531 (100)	531 (100)	53 (10.0)	478 (90.0)	
median [IQR]		12 [6;15]	14 [8;15]	12 [6;15]	0.058
≤ 2, n (%)		23 (4.3)	3 (5.7)	20 (4.2)	0.306
]2-≤5, n (%)		102 (19.2)	7 (13.2)	95 (19.9)	
]5-≤10, n (%)		112 (21.1)	8 (15.1)	104 (21.8)	
]10-≤18, n (%)		294 (55.4)	35 (66.0)	259 (54.2)	
Living donor Tx, n (%)	81 (100)	81 (100)	7 (8.6)	74 (91.3)	
median [IQR]		12 [8;15]	14 [9;16]	12 [8;14]	0.505
≤ 2, n (%)		3 (3.7)	0	3 (4.1)	0.894
]2-≤5, n (%)		13 (16.0)	1 (14.3)	12 (16.2)	
]5-≤10, n (%)		20 (24.7)	1 (14.3)	19 (25.7)	
]10-≤18, n (%)		45 (55.6)	5 (71.4)	40 (54.1)	
Recipient sex (female), n (%)					
Total population	612 (100)	264 (43.1)	24 (40.0)	240 (43.5)	0.681
Deceased donor	531 (100)	237 (44.6)	20 (37.7)	217 (45.4)	0.311
Living donor	81 (100)	27 (33.3)	4 (57.1)	23 (31.1)	0.214

IQR: interquartile range, Tx: transplantation, DGF delayed graft function

Recipient age, years	Patients with available data, n (%)	Total population	Patients with DGF	Patients without DGF	p
Pre-Tx dialysis duration (months), median [IQR]					
Total population	590 (96.4)	13.8 [7.0;24.0]	13.8 [8.2;26.1]	13.8 [6.7;23.8]	0.455
Deceased donor	514 (96.8)	14.6 [7.8;24.2]	13.7 [8.9;24.9]	14.7 [7.6;24.2]	0.824
Living donor	76 (93.8)	8.2 [5.2;16.7]	16.9 [5.2;40.9]	8.03 [5.2;15.3]	0.394
Waiting time (months), median [IQR]					
Total population	612 (100)	7.8 [3.8;14.6]	6.6 [2.4;13.6]	7.9 [3.8;14.4]	0.138
Deceased donor	531 (100)	8.4 [4.0;15.1]	6.9 [2.5;14.6]	8.8 [4.2;15.4]	0.165
Living donor	81 (100)	5.2 [2.8;9.7]	4.8 [2.3;7.5]	5.2 [2.8;9.9]	0.485

IQR: interquartile range, Tx: transplantation, DGF delayed graft function

Table 2
Ischemia times, follow-up, and outcomes

Cold ischemia time (hours), median [IQR]	**Patients with available data, n (%)**	**Total population, n = 612**	**Patients with DGF, n = 60**	**Patients without DGF, n = 552**	**p**
Total population	604 (98.7)	14.5 [11.3;17.7]	16.2 [13.7;19.6]	14.3 [11.0;17.5]	0.006
Deceased donor	528 (99.4)	15.1 [12.6;18.2]	16.9 [14.5;20.0]	15.0 [12.5;18.1]	0.004
Living donor	76 (93.8)	2.5 [1.5;3.4]	2.8 [2.5;3.6]	2.5 [1.5;3.4]	0.488
Warm ischemia time (minutes), median [IQR]					
Total population	533 (87.1)	45 [35;61]	54 [45;75]	45 [33;60]	< 0.001
Deceased donor	462 (87.0)	45 [34;62]	55 [45;75]	45 [32;60]	0.001
Living donor	71 (87.7)	43 [36;53]	50 [50;118]	41 [34;50]	0.060
Post-transplant follow-up (years), median [IQR]					
Total population	612 (100)	7.0 [4.9;10.2]	7.4 [5.0;10.0]	7.0 [4.9;10.2]	0.643
Deceased donor	531 (100)	7.2 [5.0;10.7]	7.9 [5.0;10.2]	7.1 [5.0;10.9]	0.935
Living donor	81 (100)	6.0 [4.1;8.0]	6.3 [5.8;8.3]	5.9 [4.1;8.0]	0.401
Graft loss, n (%)	612 (100)	90 (14.7)	13 (21.7)	77 (13.9)	
Cause of graft loss, n (%)	90 (100)	90 (100)	13 (14.4)	77 (85.6)	
Chronic allograft nephropathy		46 (51.1)	5 (38.5)	41 (53.2)	0.146
Acute rejection		12 (13.3)	1 (7.7)	11 (14.3)	
Recurrence of initial disease		7 (7.8)	3 (23.1)	4 (5.2)	
Infection		7 (7.8)	0	7 (9.1)	
Discontinuation of immunosuppression		3 (3.3)	0	3 (3.9)	

IQR: interquartile range, DGF: delayed graft function

Cold ischemia time (hours), median [IQR]	Patients with available data, n (%)	Total population, n = 612	Patients with DGF, n = 60	Patients without DGF, n = 552	p
Unknown		15 (16.7)	4 (30.8)	11 (14.3)	
Death during follow-up, n (%)	612 (100)	18 (2.9)	0	18 (3.3)	0.242
Lost to follow-up, n (%)	612 (100)	23 (3.8)	4 (6.7)	19 (3.4)	0.269

IQR: interquartile range, DGF: delayed graft function

Table 3
Donors' characteristics

Donor age, years	Donors with available data, n (%)	Total population	Patients with DGF	Patients without DGF	p
Total population, n (%)	612 (100)	612 (100)	60 (9.8)	552 (90.2)	
Median [IQR]		16 [12;20]	16 [11;21]	16 [12;19]	0.997
≤ 2, n (%)		21 (3.4)	4 (6.7)	17 (3.1)	0.730
]2-≤5, n (%)		44 (7.2)	4 (6.7)	40 (7.2)	
]5-≤10, n (%)		70 (11.4)	7 (11.7)	63 (11.4)	
]10-≤18, n (%)		315 (51.5)	28 (46.7)	287 (52.0)	
]18-≤30, n (%)		72 (11.8)	6 (10.0)	66 (12.0)	
]30-≤40, n (%)		42 (6.9)	5 (8.3)	37 (6.7)	
> 40, n (%)		48 (7.8)	6 (10.0)	42 (7.6)	
Deceased donor, n (%)	531 (100)	531 (100)	53 (10.0)	478 (90.0)	
Median [IQR]		15 [10;17]	15 [9;17]	15 [10;17]	0.883
≤ 2, n (%)		21 (4.0)	4 (7.5)	17 (3.6)	
]2-≤5, n (%)		44 (8.3)	4 (7.5)	40 (8.4)	0.161
]5-≤10, n (%)		70 (13.2)	7 (13.2)	63 (13.2)	
]10-≤18, n (%)		315 (59.3)	28 (52.8)	287 (60.0)	
]18-≤30, n (%)		66 (12.4)	6 (11.3)	60 (12.6)	
]30-≤40, n (%)		7 (1.3)	1 (1.9)	6 (1.3)	
> 40, n (%)		8 (1.5)	3 (5.7)	5 (1.0)	
Living donor, n (%)	81 (100)	81	7	74	
Median [IQR]		40 [35;45]	37 [34;47]	40 [35;45]	0.849
18-≤30, n (%)		6 (7.4)	0	6 (8.1)	1.000
]30-≤40, n (%)		35 (43.2)	4 (57.1)	31 (41.9)	
> 40, n (%)		40 (49.4)	3 (42.9)	37 (50.0)	

DGF: delayed graft function, eGFR: estimated glomerular filtration rate, EKFC: European Kidney Function Consortium equation

Donor age, years	Donors with available data, n (%)	Total population	Patients with DGF	Patients without DGF	p
Donor sex (female), n (%)					
Total population	612 (100)	262 (42.8)	28 (46.7)	234 (42.4)	0.583
Deceased donor	531 (100)	218 (41.1)	25 (47.2)	193 (40.4)	0.378
Living donor	81 (100)	44 (54.3)	3 (42.9)	41 (55.4)	0.697
Donor kidney side (right), n (%)					
Total population	612 (100)	273 (44.6)	32 (53.3)	241 (43.7)	0.172
Deceased donor	531 (100)	263 (49.5)	32 (53.3)	231 (48.3)	0.111
Living donor	81 (100)	10 (12.3)	0	10 (13.5)	0.588
Donor eGFR (EKFC, ml/min/1,73m²)					
Total population	603 (99)	101 [72;113]	93 [76.;112]	101 [72;113]	0.360
Deceased donor	531 (100)	94 [69;112]	88 [66;111]	95 [69;113]	0.360
Living donor	72 (89)	112 [104;117]	110 [107;117]	112 [104;117]	0.857
Log recipient/donor age					
Total population, n (%)	612 (100)	612 (100)	60 (9.8)	552 (90.2)	
-5 to -3 (ratio ≤ 1/8)		21 (3.4)	2 (3.2)	19 (3.4)	0.097
]-3 to -2 (1/8 < ratio ≤ 1/4)		58 (9.5)	7 (11.7)	51 (9.2)	
]-2 to -1 (1./4 < ratio ≤ 1/2)		171 (27.9)	12 (20)	159 (28.8)	
]-1 to 0 (1/2 < ratio ≤ 1)		205 (33.5)	17 (28.3)	188 (34.1)	
]0 to 1 (1 < ratio ≤ 2)		113 (18.5)	16 (26.7)	97 (17.6)	
]1 to 2 (2 < ratio ≤ 4)		23 (3.8)	2 (3.3)	21 (3.8)	
]2 to 3 (4 < ratio ≤ 8)		14 (2.3)	1 (1.7)	13 (2.4)	

DGF: delayed graft function, eGFR: estimated glomerular filtration rate, EKFC: European Kidney Function Consortium equation

Donor age, years	Donors with available data, n (%)	Total population	Patients with DGF	Patients without DGF	p
]3 to 4 (8 < ratio ≤ 16)		7 (1.1)	3 (5.0)	4 (0.7)	
Deceased donor, n (%)	531 (100)	531 (100)	53 (10.0)	478 (90.0)	
-5 to -3 (ratio ≤ 1/8)		9 (1.7)	2 (3.8)	7 (1.5)	0.053
]-3 to -2 (1/8 < ratio ≤ 1/4)		37 (7.0)	4 (7.5)	33 (6.9)	
]-2 to -1 (1./4 < ratio ≤ 1/2)		126 (23.7)	8 (15.1)	118 (24.7)	
]-1 to 0 (1/2 < ratio ≤ 1)		202 (38.0)	17 (32.1)	185 (38.7)	
]0 to 1 (1 < ratio ≤ 2)		113 (21.3)	16 (30.2)	97 (20.3)	
]1 to 2 (2 < ratio ≤ 4)		23 (4.3)	2 (3.8)	21 (4.4)	
]2 to 3 (4 < ratio ≤ 8)		14 (2.6)	1 (1.9)	13 (2.7)	
]3 to 4 (8 < ratio ≤ 16)		7 (1.3)	3 (5.7)	4 (0.8)	
Living donor, n (%)	81 (100)	81 (100)	7 (8.6)	74 (91.4)	
-5 to -3 (ratio ≤ 1/8)		12 (14.8)	0	12 (16.2)	0.605
]-3 to -2 (1/8 < ratio ≤ 1/4)		21 (25.9)	3 (42.9)	18 (24.3)	
]-2 to -1 (1./4 < ratio ≤ 1/2)		45 (55.6)	4 (57.1)	41 (55.4)	
]-1 to 0 (1/2 < ratio ≤ 1)		3 (3.7)	0	3 (4.1)	
Donor/recipient age difference (years), median [IQR]					
Total population	612 (100)	4 [-1;11]	3 [-2;12]	4 [0;11]	0.256
Deceased donor	531 (100)	3 [-1;8]	1 [-3;9]	3 [-1;8]	0.218
Living donor	81 (100)	30 [25;34]	32 [25;34]	30 [26;34]	0.913

DGF: delayed graft function, eGFR: estimated glomerular filtration rate, EKFC: European Kidney Function Consortium equation

Variables associated with DGF occurrence

According to the logistic regression model, each additional hour of cold ischemia increased the OR of DGF by 7% (p = 0.022) and each additional minute of warm ischemia increased the OR of DGF by 1% (p =

0.002; Table 4). One center reported a significantly shorter WIT than the others: 28 [23;33] vs. 50 [40;68] minutes (p < 0.001) and a lower frequency of DGF 1.8 vs. 11.6% (OR 0.14, 95%CI 0.02–0.46; p = 0.007).

Table 4
Factors associated with DGF

Donor type, ref: deceased	**Univariable OR [95%CI]**	**p**	**Multivariable OR [95%CI]**	**p**
	0.85 [0.34;1.83]	**0.706**	**3.32 [0.87;12.14]**	**0.072**
Donor age (years), ref: ≤2 years				
]2-≤5	0.42 [0.09;1.98]	0.263		
]5-≤10	0.47 [0.13;1.97]	0.273		
]10-≤18	0.41 [0.14;1.52]	0.136		
]18-≤30	0.39 [0.10;1.65]	0.175		
]30-≤40	0.57 [0.14;2.57]	0.449		
]40-≤71	0.61 [0.15;2.62]	0.480		
Donor sex, ref: female	0.84 [0.49;1.44]	0.525		
Recipient age (years), ref: ≤2 years				
]2-≤5	0.57 [0.15;2.77]	0.436		
]5-≤10	0.56 [0.15;2.67]	0.412		
]10-≤18	1.03 [0.34;4.46]	0.968		
Recipient /donor age ratio	1.19 [0.97;1.46]	0.099	1.22 [0.96;1.55]	0.106
Recipient sex, ref female	1.15 [0.67;2.01]	0.606		
Pre-Tx dialysis duration (years)	1.05 [0.89;1.21]	0.524		
Donor eGFR (EKFC, ml/min/1,7”m²)	0.60 [0.23;1.55]	0.285		
Transplant center		0.036[a]		
Cold ischemia time (hours)	1.05 [1.00;1.10]	0.031	1.07 [1.01;1.14]	0.022
Warm ischemia time (minutes)	1.01 [1.01;1.02]	< 0.001	1.01 [1.00;1.02]	0.002

Ref: reference, Tx: transplantation, [a] Analysis of Deviance, eGFR: estimated glomerular filtration rate, EKFC: European Kidney Function Consortium equation

There was no significant association between both recipient and donor age and DGF occurrence. Although not statistically significant, a higher ratio of recipient to donor age is associated with an increased risk of DGF both in univariable (OR 1.19, 95%CI 0.97–1.46, p = 0.099) and multivariable analysis (OR 1.22, 95%CI 0.96–1.55; p = 0.106) (Table 4). Of note, 157 (25.7%) children were older than their donor, of whom 22 (14.0%) presented a DGF, whereas 455 (74.3%) were as old or younger than their donor, of whom 38 (8.4%) presented a DGF (OR 1.70, 95%CI 0.98–2.93, p = 0.055; Fig. 2).

In univariable analysis, there was no association between the type of donor and the occurrence of DGF. In multivariable analysis, living donor Tx was associated with an increased risk of DGF (OR 3.32, 95%CI 0.87–12.14, p = 0.072; Table 4) without reaching statistical significance.

DGF and graft survival

The estimated graft survival was not significantly different in the population between patients with and without DGF (Fig. 3). These results were confirmed by the multivariable Cox proportional hazard model (adjusted HR 1.37, 95%CI 0.74–2.55, p = 0.315; Table 5). However, DGF duration was associated with graft survival in univariable analysis (HR 1.06, 95%CI 1.01–1.12, p = 0.013) among children who experienced DGF. After categorization of DGF duration in two classes (≤ 14 days and > 14 days), graft survival was not significantly associated with longer DGF (suppl Fig. 1). Of note there was no difference of allograft survival according to center (Table 5).

Table 5
Factors associated with graft survival in the study population (n = 612)

Delayed graft function	**Univariable HR [95%CI]**	**p**	**Multivariable HR [95%CI]**	**p**
	1.53 [0.85;2.75]	**0.158**	**1.37 [0.74;2.55]**	**0.315**
Donor type, ref: deceased	2.20 [1.31;3.70]	0.003	5.71 [2.25;14.53]	< 0.001
Donor age (years), ref: ≤2 years				
]2-≤5	0.63 [0.15;2.62]	0.520		
]5-≤10	0.70 [0.19;2.64]	0.600		
]10-≤18	0.87 [0.27;2.80]	0.813		
]18-≤30	1.47 [0.43;5.09]	0.541		
]30-≤40	1.41 [0.36;5.44]	0.622		
]40-≤71	1.97 [0.55;7.07]	0.299		
Recipient age (years), ref: ≤2 years				
]2-≤5	0.87 [0.25;3.09]	0.830		
]5-≤10	1.13 [0.33;3.84]	0.842		
]10-≤18	1.45 [0.45;4.64]	0.528		
Recipient /donor age ratio	0.92 [0.78;1.09]	0.358		
Pre-Tx dialysis duration (years)	1.10 (0.98;1.24)	0.102		
Transplant center		0.817[a]		
Left side kidney donor	1.29 [0.84;1.96]	0.241		
Cold ischemia time (hours)	1.00 [0.97;1.04]	0.783	1.06 [1.02;1.11]	0.008
Warm ischemia time (minutes)	1.00 [0.99;1.01]	0.952		
A, B, DR, DQ HLA mismatches number	1.07 [0.91;1.26]	0.414	1.20 [1.01;1.43]	0.041
Idiopathic Nephrotic syndrome as primary disease	1.59 [0.97;2.62]	0.068	1.63 [0.98;2.71]	0.062

Ref: reference, [a] Analysis of Deviance

Discussion

The frequency of DGF we observed (9.8%) is comparable to that reported for non-preemptive brain dead donor Tx from 2014 to 2016 in OPTN: 11.1% [18] and from 2000 to 2014 in the United Kingdom: 10% [19]. As others [15, 19], we decided to exclude PNF, which are mainly due to vascular thrombosis, as reported herein (the cause of three-quarters of graft loss among patients with PNF but none among those with DGF included) and elsewhere [36]. This choice was made to allow evaluating the causes and consequences of a transient graft dysfunction using a simple DGF definition retained by a majority of studies and available in the French population-based registry (5).

We observed a median DGF duration of 5.5 [3.0;9.3] days that is shorter than in the pediatric cohort of ANZDATA registry (8 [14] days) [13] and shorter than reported in most adult series: 5 [2;13] [37], 7 [9] [38], 6 [2;13] [39] and 10 [6;15] [40] with a proportion of patients with DGF duration > 14 days lower in our series: 10% versus 20% [37], 24% (period 2018–2021) [41], 25% (≥ 14 days) [38], 26% [40] and 31% [42, 43] in adults series. This shorter duration of DGF probably explains the lack of a significant association found between DGF and graft survival in our study, whereas a longer duration of DGF is recognized as being associated with poorer graft survival in adults, particularly when it exceeds 14 days [8, 37–39, 43]. In pediatrics, Boussetta et al, in their single-center study of kidney Tx between 1989 and 2022 conducted in Tunisia, reported a non-significant difference in graft survival [44] as did Cesca et al. in a single-center study from Italy [10]. Contrary to these single-center studies, Parker et al. [12], in a multicenter pediatric study in the US, reported that, in deceased donor kidney Tx between 2006 and 2016, graft survival is significantly lower when a DGF occurs; as did Peticca et al. considering the period from 1994 to 2022 [14], and Lim et al. in Australia-New Zealand between 1990 and 2012 [13]. These authors [12–14] reported an association between DGF and decreased allograft survival despite the exclusion of graft loss occurring the first seven days post-transplantation. In our study, there was no significant association between DGF and graft survival in the total population. A recent study in adults shows that graft loss associated with DGF, independent of donor characteristics, is limited to the early posttransplant period [45].

The association between longer WIT and the occurrence of DGF observed herein in a pediatric cohort has been reported in adult studies [8, 46]. Optimizing surgical techniques, with shorter WIT, is feasible as shown in one of the centers that participated in the present study and was associated with a lower frequency of DGF. The association between longer CIT and the occurrence of DGF has also been reported in adult [7, 8, 40, 47] and pediatric studies [20, 44]. Kidneys from older living donors (> 50 years old) seem particularly sensitive to CIT: every additional hour of CIT has been shown to be associated with adjusted odds ratio of 1.28 (95%CI 1.07–1.53, p = 0.007) for DGF in this population [25].

In addition to these similarities the results of the present study differ in certain regards to that reported elsewhere. For instance, although non-statistically significant, living donation may be associated with a higher odd of DGF. However, most other studies that report data from pediatric registries found a lower rate of DGF in pediatric kidney transplant recipients from living donors [11, 15, 19, 20, 33]. Several reasons could explain this discrepancy. The first concerns the low frequency of living donation in our study (13%) compared to 40% in the UNOS [15], 45% in the UK [19], 65% in ANZDATA [33] and 33% in the

CERTAIN registries [20]. The second, is the young age of deceased donors in our study (median [IQR] 15 [10–17] years; mean ± SD age of 14.4 ± 7.7 years, *data not shown*) compared to 29 ± 13 in the UK [19], 35.0 ± 16.8 years in the ANZDATA registries [33] and a median of 22 years in the SRTR [18]. In parallel, the mean ± SD age of living donors (40.4 ± 6.9 years) was equivalent to that reported elsewhere: 40 ± 8 years in the UK [19], 42.2 ± 9.1 years in the ANZDATA [33], and 37 years in the UNOS registries [11]. Thus, the important difference of age between deceased and living donors in the present study could explain difficulties of the multivariable model to take into account donor age and may participate to the higher risk of DGF observed after living donation. The individual impact of living donation would therefore deserve further investigation.

Another difference is the possible association between an increased recipient/donor age ratio and the occurrence of DGF. Kostakis et al. did not report any association between DGF and the ratio of donor body surface area (BSA) over recipient BSA [15], but the population included in their study was different than ours: 40% living donors, mean donor age 28.7 ± 11.3 vs 17.9 ± 11.6 years in our population, and 10.2% of donors with a lower BSA than the recipient while 25.7% of those from our study were younger than their recipient [15]. In the same way, Lim et al did not find any association between recipient/donor BSA ratio and DGF in a population of deceased donor kidney transplant recipients aged 21 years or younger, but again donors were more than twice as old in their population as in ours [13]. In addition, Trnka et al. reported an increased frequency of DGF in case of higher difference of age between donor and recipient [33], but in a transplant population that was even more different to that included here; 65% of living donation, a mean donor age of 40.0 ± 12.7 years and a donor/recipient age difference of 29 [23–35] vs 4 [-1 to 11] years in our study.

The study presented here has several limitations. First, we considered only graft survival among the potential consequences of DGF, without assessing other consequences, such as psychological effects, additional costs, length of hospital stay and increased workload for the teams. Second, the number of transplants and the number of cases of DGF are probably insufficient to confirm associations between DGF and type of donation or recipient-to-donor age ratio. Third, the low rate of living donor transplant rate and the young age of deceased donors in our population which are distinctive of the French pediatric kidney Tx population limit the generalizability of our findings. Nevertheless, the population-based and multicentre nature of our pediatric population, and the description of the duration of DGF, constitute, in our view, important strengths of this study.

Conclusion

Longer cold and warm ischemia times are risk factors for DGF in pediatric kidney transplantation. No significant effect of DGF on graft survival was found in our cohort but DGF duration was overall short and was associated with reduced graft survival among recipients with DGF. Strategies aimed at reducing ischemia times may reduce the incidence of DGF.

Declarations

Authors do not have any financial or non-financial interests that are directly or indirectly related to this work.

Data availability:

The data that support the findings of this study are available on request from the corresponding author

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Figures

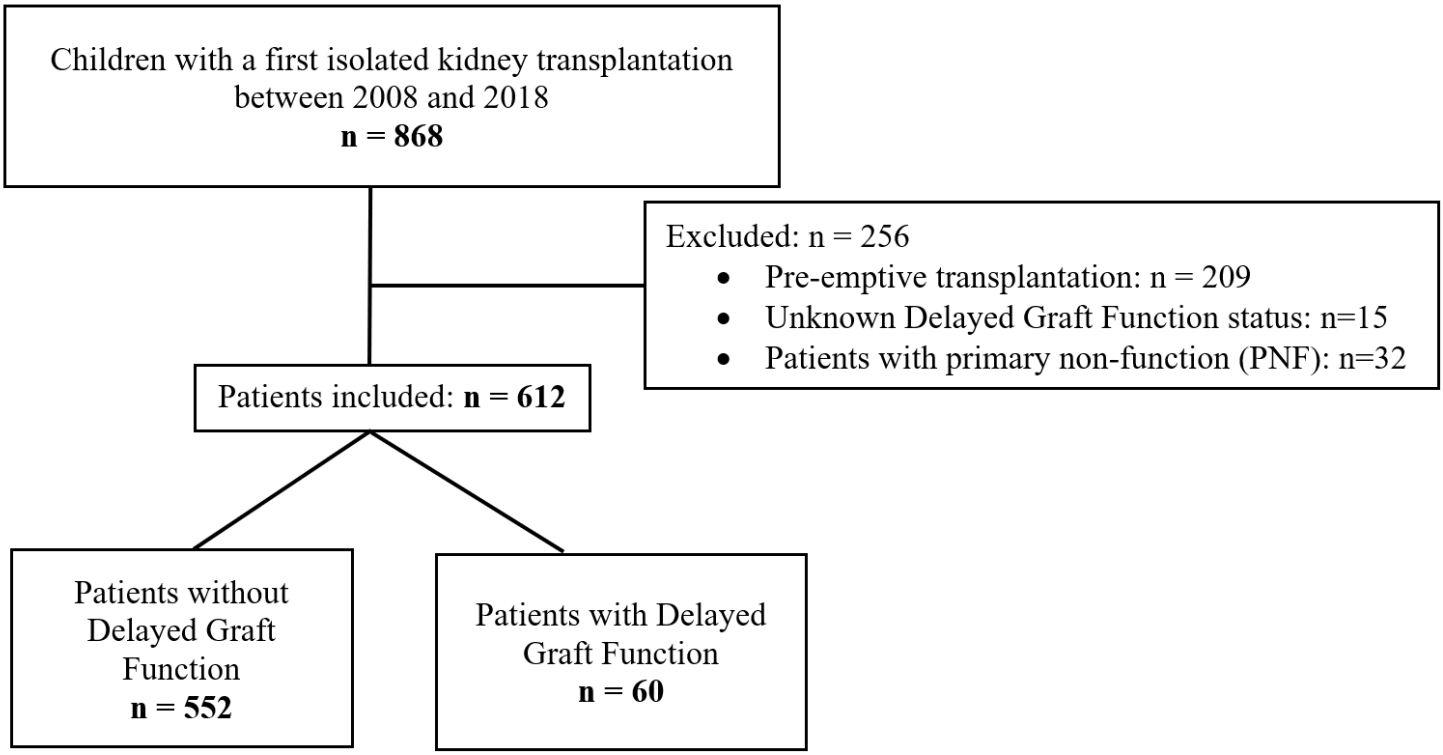


Figure 1

Study flow chart

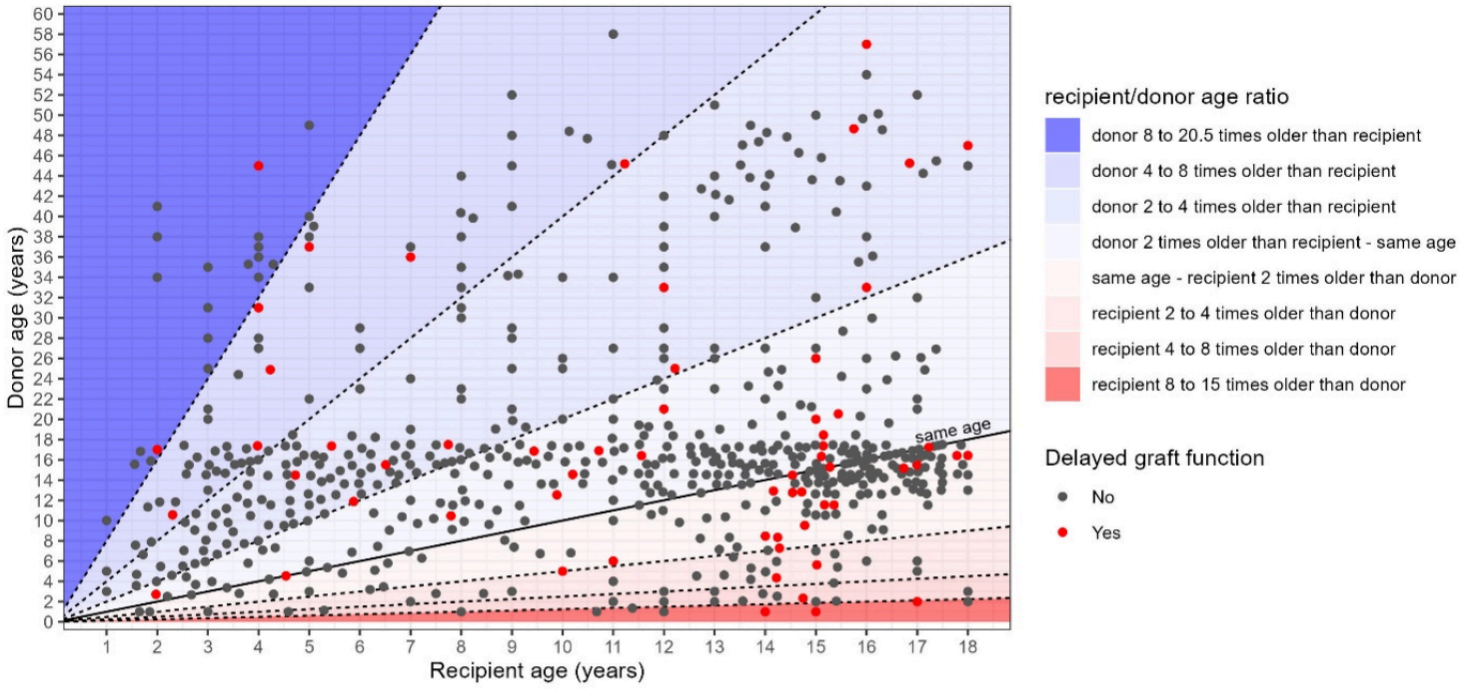


Figure 2

Donor Age, recipient age, recipient/donor age ratio, and delayed graft function. DGF rate increases with higher recipient/donor age ratio: 4/21 (19,0%) if recipient 4 to 15 times older than donor, 22/157 (14.0%) if ratio>1 (recipient older than donor), and 38/455 (8.4%) if ratio ≤1 (recipient as old or younger than donor) (Tables 3 and 4)

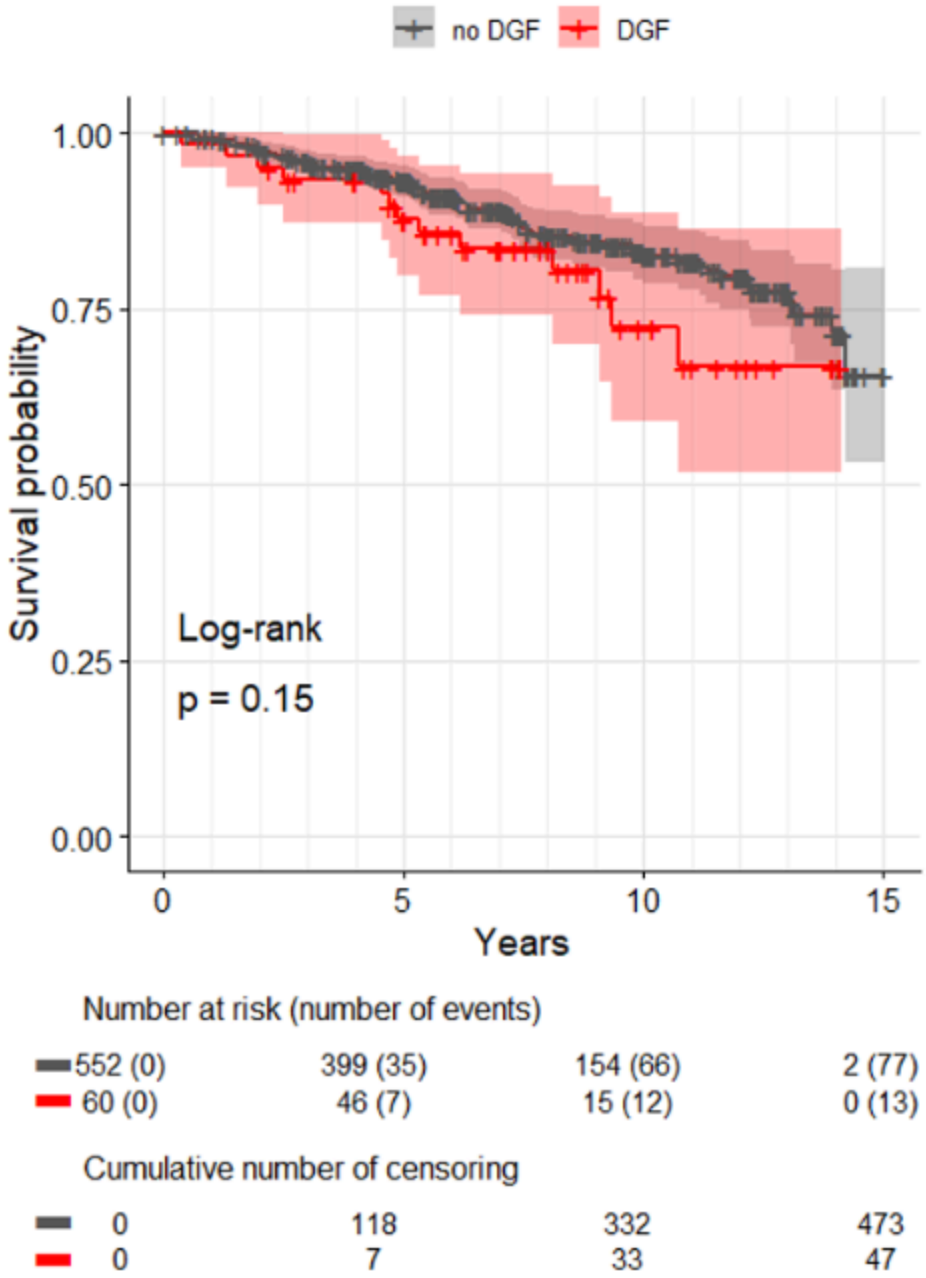


Figure 3

Graft survival after a first isolated non-preemptive transplantation according to delayed graft function (Kaplan-Meier curves with 95% Confidence Intervals)

Supplementary Files

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