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Retrospective Cohort Study

## Preemptive living donor kidney transplantation: Access, fate, and review of the status in Egypt

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### Abstract

#### BACKGROUND

Preemptive living donor kidney transplantation (PLDKT) is recommended as the optimal treatment for end-stage renal disease.

#### AIM

To assess the rate of PLDKT among patients who accessed KT in our center and review the status of PLDKT in Egypt.

#### METHODS

We performed a retrospective review of the patients who accessed KT in our center from November 2015 to November 2022. In addition, the PLDKT status in Egypt was reviewed relative to the literature.

#### RESULTS

Of the 304 patients who accessed KT, 32 patients (10.5%) had preemptive access to KT (PAKT). The means of age and estimated glomerular filtration rate were  $31.7 \pm 13$  years and  $12.8 \pm 3.5$  mL/min/1.73 m<sup>2</sup>, respectively. Fifty-nine patients had KT, including 3 PLDKTs only (5.1% of total KTs and 9.4% of PAKT). Twenty-nine patients (90.6%) failed to receive PLDKT due to donor unavailability (25%), exclusion (28.6%), regression from donation (3.6%), and patient regression on starting dialysis (39.3%). In multivariate analysis, known primary kidney disease ( $P = 0.002$ ), patient age ( $P = 0.031$ ) and sex ( $P = 0.001$ ) were independent predictors of achievement of KT in our center. However, PAKT was not significantly ( $P = 0.065$ ) associated with the achievement of KT. Review of the literature revealed

lower rates of PLDKT in Egypt than those in the literature.

## CONCLUSION

Patient age, sex, and primary kidney disease are independent predictors of achieving living donor KT. Despite its non-significant effect, PAKT may enhance the low rates of PLDKT. The main causes of non-achievement of PLDKT were patient regression on starting regular dialysis and donor unavailability or exclusion.

**Key Words:** Access to kidney transplantation; Donor regression; Kidney transplantation; Living donors; Preemptive kidney transplantation; Transplantation

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**Core Tip:** Patients with preemptive access to kidney transplantation (PAKT) may have significant differences from those with conventional access to KT, warranting more evaluation. In this study, known primary kidney disease was an independent factor of achievement of living donor KT (LDKT). In addition, the older age and female sex were independent predictors of non-achievement of LDKT. However, unavailability, regression, and exclusion of LDs and patient regression on starting dialysis may prevent achievement of preemptive LDKT (PLDKT) in patients with PAKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The current literature review may refer to that PLDKT has comparable or variably better outcomes than the conventional LDKT. Hence, PLDKT is recommended as the first choice for each candidate patient. In Egypt, the rate of PLDKT is still lower than that of other countries, warranting implementation of effective strategies to promote PLDKT.

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## INTRODUCTION

Preemptive kidney transplantation (PKT) is defined as receiving kidney transplantation (KT) before initiation of maintenance dialysis in patients with end-stage renal disease (ESRD)[1,2]. This definition may vary from one KT program to another, where patients who receive dialysis sessions sporadically or as conditioning pre-transplantation sessions for no more than 1 wk may be included in this definition[2-6]. The evolution of PKT was more than 30 years ago[7], when it passed through an insidious course and gained variably insufficient interests among the physicians and surgeons in the KT community[1,5]. Many initiatives and programs have been triggered to promote PKT, especially in the sector of living donor kidney transplantation (LDKT). These initiatives promote living kidney donation (LKD) programs as the most effective contributor to PKT[4-7]. PKT is a time-based KT strategy controlled by setting the timing of KT surgery at a point just before the start of regular dialysis as much as possible. This philosophy represents the natural course of management of most diseases. However, it has generated debate along the different axes of KT, such as the proposed lead-time bias effect on the outcomes of PKT[8]. The incidence of PKT has improved gradually from 2% in its early years to 6%-7% in the last years. Most cases come from LDKT programs, where it may reach up to 34% in some countries that adopt LDKT programs[6,9]. The latter percentage refers to the fundamental role of LD in the promotion of PKT strategy[10]. Preemptive access to KT (PAKT) and waitlisting are other effective contributors to PKT. Hence, they are fundamental issues in PKT literature[1,11]. However, they have mostly been ignored in research from Egypt, where only LDKT is performed in adults[9,12-14] and pediatrics[15-17].

We assessed the percentage of patients with PAKT and their fate regarding the receipt of preemptive LDKT (PLDKT).

## MATERIALS AND METHODS

### Study design

A retrospective review was performed for the electronic and manual records of patients with ESRD who sought LDKT in our center from November 2015 to November 2022. The study included both patients with PAKT, which was defined as the presentation of a patient with chronic kidney disease (CKD) stage 4 or 5 for KT prior to the start of regular dialysis and those with conventional access to KT (CAKT). The exclusion criterion was patients who refused KT before starting the preparation for LDKT (Figure 1). The relevant demographic characteristics of the patients and potential donors including age, sex, and relatedness to the potential donors were reviewed. Also, the clinical data including the primary kidney disease, estimated glomerular filtration rate (eGFR) at presentation, outcomes of preparation to KT, causes of deferring LDKT, and fate of the patients and donors were studied. We used the CKD-Epidemiology Collaboration creatinine equation to estimate eGFR for patients with PAKT[18].

Also, a review of the literature was performed to assess PLDKT in KT studies from Egypt. The KT center volume, pre-KT characteristics, and percentages and outcomes of PLDKT were reviewed. Furthermore, the literature was reviewed for the incidence of PLDKT in studies from other countries and large-volume KT registries.

This study was conducted as a topic in a KT research project regarding the outcomes of LDKT at our center. The institutional review board number is 17200148/2017.

### Statistical analysis

Statistical analyses were performed with EasyMedStat (version 3.21.4; [www.easymedstat.com](http://www.easymedstat.com)). Continuous variables are presented as the mean  $\pm$  standard deviation and range. However, categorical variables are presented as the number and percentage of each category. We created two groups (PAKT and CAKT) according to the status of dialysis at the time of access to transplantation. Normality and heteroskedasticity of continuous data were assessed with the White test (or with Shapiro-Wilk in multivariate analysis) and Levene's test, respectively. Continuous outcomes were compared with the unpaired Student *t*-test, Welch *t*-test, or Mann-Whitney *U* test according to the data distribution. Categorical outcomes were compared with the chi-squared or Fisher's exact test accordingly. Multivariate logistic regression was performed to assess the factors contributing to achievement of KT in our center. Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique.  $P < 0.05$  was considered statistically significant.

## RESULTS

Between November 2015 and November 2022, 325 patients attended our center for KT. Twenty-one (6.5%) patients changed their mind or were not serious in accessing KT. The remaining 304 patients were differentiated into PAKT and CAKT groups (Figure 1). The former group included 32 patients (10.5%) who were not on dialysis at the time of access to KT and the latter group included 272 (89.5%) patients with a mean (range) duration of hemodialysis of  $6.3 \pm 10.5$  (0.5–108) mo. Both groups were compared for their demographic and clinical characteristics (Table 1). Follow-up after regression or exclusion decision varied from 3 mo to 6 years.

In the PAKT group, 29 patients (90.6%) failed to receive PLDKT due to original donor unavailability (25%), exclusion (28.6%), regression (3.6%), financial causes (3.6%), and patients' regression from KT when starting regular dialysis (39.3%) (Table 1). Hence, PLDKT was carried out in 3 patients only, representing 5.1% of the total KTs and 9.4% of patients with PAKT. One of these three patients died from complications of the coronavirus disease 2019, 6 mo after KT. The other 2 patients were still living with a functioning graft for 68 and 12 mo at the time of writing of this article. The detailed characteristics of patients with PAKT are presented as individual patients (Table 2). The mean (range) age was  $31.7 \pm 13$  (13–60) years. Most of the patients presented with stage 5 CKD. The mean (range) for serum creatinine level and eGFR was  $6 \pm 1.6$  (3.2–9.8) mg/dL and  $12.8 \pm 4.8$  (7–28) mL/min/1.73 m<sup>2</sup>, respectively.

In the current cohort of patients, the total number of patients who had been transplanted at our center (59 patients) or at other centers (29 patients) was 88 (28.9%) patients. In a comparison between the patients who achieved (59 patients) and those who failed to achieve (245 patients) LDKT in our center, there were significant differences in age ( $P = 0.034$ ), sex ( $P < 0.001$ ), primary kidney disease ( $P = 0.008$ ), number of potential donors ( $P = 0.003$ ), and acceptance/exclusion rate of evaluated donors ( $P < 0.001$ ) per patient (Table 3).

In multivariate analysis, known primary kidney disease ( $P = 0.002$ ) was associated with higher rates of achievement of KT in our center. In addition, female sex ( $P = 0.001$ ) and older patients ( $P = 0.031$ ) were significantly associated with lower rates of achievement of KT in our center. However, PAKT ( $P = 0.065$ ) and multiple potential donors ( $P = 0.529$ ) were not significantly associated with the rate of achievement of KT in our center (Table 4).

**Table 1 A comparison of the demographic and clinical characteristics of the patients with preemptive access to kidney transplantation and those with conventional access to kidney transplantation, *n* (%)**

Variables	PAKT, <i>n</i> = 32	CAKT, <i>n</i> = 272	<i>P</i> value
Age in yr, mean $\pm$ SD (range)	31.7 $\pm$ 13 (13-60)	32.1 $\pm$ 11.5 (12-66)	0.677
Sex			
Men	22 (68.8)	213 (78.3)	0.263
Women	10 (31.2)	59 (21.7)	
Primary kidney disease			
Glomerulonephritis	3 (9.4)	8 (2.9)	< 0.001
Hereditary disease	3 (9.4)	6 (2.2)	
Obstructive uropathy	4 (12.5)	8 (2.9)	
Systemic disease	4 (12.5)	14 (5.2)	
Urolithiasis	3 (9.4)	7 (2.6)	
Unknown	15 (46.9)	229 (84.2)	
Number of potential donors <sup>1</sup>			
Patients presented without donors	8 (25)	36 (13.2)	0.088
With one donor	17 (53.1)	187 (68.8)	
With two donors	4 (12.5)	40 (14.7)	
With three donors	3 (9.4)	9 (3.3)	
Donor evaluation	24	236	
Patients with evaluated donors	20	194	
With accepted donor(s)	10 (50)	89 (45.9)	0.232
With one donor excluded	7 (35)	75 (38.7)	
With two donors excluded	0 (0)	15 (7.7)	
With three donors excluded	1 (5)	2 (1)	
With excluded and accepted donors	2 (10)	13 (6.7)	
Number of not evaluated donors per patient	6	56	
One donor	3 (50)	51 (91.1)	0.024
Two donors	3 (50)	4 (7.1)	
Three donors	0 (0)	1 (1.8)	
Order of the accepted donor	12	102	
First	10 (83.3)	87 (85.3)	0.634
Second	1 (8.3)	11 (10.8)	
Third	1 (8.3)	4 (3.9)	
Accepted donor age (yr), mean $\pm$ SD (range)	38.1 $\pm$ 9 (25-53)	40.6 $\pm$ 10.4 (21-60)	0.39
Patient-donor relatedness degree			
First	5 (41.7)	55 (53.9)	0.234
Second	5 (41.7)	40 (39.2)	
Third	1 (8.3)	6 (5.9)	
Unrelated	1 (8.3)	1 (1)	
Sex of accepted donors			
Women	7 (58.3)	66 (64.7)	0.754
Men	5 (41.7)	36 (35.3)	



Accepted donor commitment			
Donated	4 (33.3)	55 (53.9)	0.171
Regressed	1 (8.3)	16 (15.7)	
Released	7 (58.3)	31 (30.4)	
Number of excluded donors per patient			
One donor	7 (77.8)	84 (80)	0.262
Two donors	1 (11.1)	19 (18.1)	
Three donors	1 (11.1)	2 (1.9)	
Main causes of donor exclusion			
Medical causes	1 (10)	51 (51.5)	0.027
Immunologic mismatch	7 (70)	34 (34.3)	
Combined medical and immunologic	2 (20)	14 (14.1)	
Main causes of donor release			
Financial causes	0 (0)	3 (10.7)	0.235
Patient death	0 (0)	3 (10.7)	
Patient non-candidacy	0 (0)	10 (35.7)	
Patient regression	5 (100)	12 (42.9)	
Achievement of kidney transplantation			
Failed	25 (78.1)	191 (70.2)	0.568
Transplanted in our center	4 (12.5)	55 (20.2)	
Transplanted in another center	3 (9.4)	26 (9.6)	
Cause of non-achievement of transplantation in our center			
Donor exclusion	8 (28.6)	88 (40.6)	0.035
Donor regression	1 (3.6)	16 (7.4)	
Donor unavailability	7 (25)	37 (17.1)	
Financial causes	1 (3.6)	13 (5.6)	
Patient non-candidacy	0 (0)	25 (11.5)	
Patient death	0 (0)	5 (2.6)	
Patient regression	11 (39.3)	33 (15.2)	
Fate of recipients who failed to have transplantation in our center			
Death	0 (0)	13 (6)	0.213
On hemodialysis	24 (85.7)	147 (67.7)	
Transplantation in another center	3 (10.7)	26 (12)	
Unknown	1 (3.6)	31 (14.3)	

<sup>1</sup>The headings of the donor evaluation and non-evaluation may include overlapping numbers due to different outcomes of the evaluation of multiple donors, resulting in non-complementary values relative to the total number of patients in both groups.

CAKT: Conventional access to kidney transplantation; PAKT: Preemptive access to kidney transplantation; SD: Standard deviation.

Review of the literature for PLDKT in studies from Egypt revealed that only eight articles addressed PLDKT (Table 5). These articles were from three academic centers only, including seven original research and one opinion article. The percentage of PLDKT varied between 6.4% in adults and 23% in pediatrics. No articles addressed the PAKT or waitlisting. The reported patient and graft survival rates were similar to those of conventional LDKT (CLDKT) in the literature.

In addition, a review of the English literature for the incidence of PLDKT in other countries revealed higher rates than those from Egypt. However, they reported on PKT from both LDs and deceased donors. There were higher rates of PKT in patients who received LDKT than in those who received deceased donor KT (Table 6). In 1987, Migliori *et al* [19] were the first to evaluate the effects and



**Table 2 Detailed characteristics and fate of patients with preemptive access to kidney transplantation, *n* = 32**

Case Number	Age in yr	Sex	No. of Potential donors relatedness	Primary kidney disease	Serum creatinine in mg/dL	Stage of CKD, eGFR as mL/min/1.73 m <sup>2</sup>	PLDKT receipt	Cause of cancelled PLDKT	Fate of the patient
Case 1	48	Male	3 (Wife, Sister, daughter)	Unknown	8.5	5 (7)	None	Donor exclusion	On HD for 20 m then CLDKT in our center
Case 2	25	Male	1 (Mother)	CMU	5.5	5 (14)	None	Donor exclusion	On HD for 62 m
Case 3	28	Male	3 (Brothers)	Unknown	8.2	5 (8)	None	Patient regression	On HD for 74 m
Case 4	59	Female	2 (Sons)	Diabetic nephropathy	5.4	5 (11)	None	Patient regression	On HD 75 m
Case 5	47	Male	2 (Unrelated)	ADPCKD	4.8	5 (14)	Yes	NA	Living with a functioning graft for 68 m
Case 6	26	Male	1 (Brother)	Urolithiasis	7.8	5 (9)	None	Patient regression	On HD then lost to follow up
Case 7	27	Male	1 (Aunt)	Unknown	6.9	5 (10)	None	Patient regression	On HD then CLDKT in another center
Case 8	38	Male	1 (Unrelated)	ADPCKD	7.4	5 (9)	None	Donor exclusion	On HD for 34 m
Case 9	22	Female	None	Unknown	4.8	5 (12)	None	Donor unavailability	On HD for 33 m
Case 10	19	Female	None	Unknown	3.5	4 (19)	None	Donor unavailability	On HD for 24 m
Case 11	24	Male	None	GN	4.4	4 (18)	None	Donor unavailability	On HD then lost to follow-up
Case 12	13	Male	1 (Mother)	Congenital VURD	4.6	4 (18)	Yes	NA	Died from COVID-19 complications
Case 13	14	Male	1 (Mother)	PUV	5.3	4 (16)	None	Donor exclusion	On HD then CLDKT in another center
Case 14	23	Male	1 (Mother)	Urolithiasis	5.1	5 (15)	None	Patient regression	On HD for 18 m
Case 15	34	Female	1 (Sister)	Unknown	8.6	5 (8)	None	Donor regression	On HD for 6 m before death
Case 16	52	Male	1 (Brother)	ADPCKD	6.2	5 (10)	None	Donor exclusion	On HD for 28 m
Case 17	19	Male	None	VURD	3.2	4 (28)	None	Donor unavailability	On HD 24 m
Case 18	36	Male	1 (Sister)	Hypertensive nephropathy	6.8	5 (10)	None	Patient regression	On HD for 26 m
Case 19	34	Male	3 (Unrelated)	ADPCKD	7.5	5 (9)	None	Donor exclusion	On HD for 27 m
Case 20	34	Male	2 (Brother, Sister)	Diabetic nephropathy	8.4	5 (8)	None	Patient regression	On HD for 28 m
Case 21	15	Male	1 (Mother)	Unknown	5.4	5 (15)	None	Donor exclusion	On HD for 6 m then lost to follow-up
Case 22	44	Male	1 (Brother)	Urolithiasis	6.7	5 (10)	None	Patient regression	On HD for 8 m then lost to follow-up
Case 23	40	Female	1 (Cousin)	Unknown	6.7	5 (7)	None	Donor regression	Unknown
Case 24	44	Male	1 (Brother)	Hyperuricemia	5.6	5 (12)	None	Donor exclusion	On HD for 13 m
Case 25	19	Male	1 (Mother)	Congenital	4.7	4 (17)	Yes	NA	Living with a

VURD									functioning graft for 12 m
Case 26	23	Female	1 (Mother)	Unknown	6.3	5 (12)	None	Patient regression	On HD for 18 m
Case 27	60	Male	None	Unknown	5.6	5 (11)	None	Donor unavailability	On HD then CLDKT in another center
Case 28	29	Male	1 (Sister)	GN	3.9	4 (19)	None	Donor exclusion	On HD 8 m
Case 29	25	Female	1 (Brother)	Unknown	9.8	5 (7)	None	Patient regression	On HD for 6 m
Case 30	47	Female	None	Unknown	6.4	5 (12)	None	Patient regression	On HD for 16 m
Case 31	25	Male	None	FSGS	4.5	4 (18)	None	Donor unavailability	On HD for 5 m
Case 32	21	Female	None	Unknown	4.2	4 (18)	None	Donor unavailability	On HD for 3 m

ADPCKD: Autosomal dominant polycystic kidney disease; CKD: Chronic kidney disease; CLDKT: Conventional living donor kidney transplantation; CMU: Congenital megaureter; COVID-19: Coronavirus disease 2019; eGFR: Estimated glomerular filtration rate; FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; HD: Hemodialysis; N/A: Not applicable; PLDKT: Preemptive living donor kidney transplantation; PUV: Posterior urethral valve; VURD: Vesicoureteral reflux disease.

outcomes of PKT in a large study from the United States, reporting a PKT rate of 7.6%. They were followed by two European studies with variable rates[20,21]. Then, five studies presented data from registries from United States and Canada and reported higher PKT rates up to 21% of the total KT and more than 29% of LDKTs[22-26]. In addition, three studies from Japan, Australia, and Korea presented PLDKT rates up to 22% in patients receiving LDKT[27-29]. In 2009, two studies of mixed LD and deceased donor KT showed higher rates of PLDKT about 39%[30,31]. Between 2011 and 2016, five studies of pediatric and adult KT showed similar rates[2,32-35]. In the last 3 years, many studies have reported high PLDKT rates more than 34% of LDKTs[36-38].

## DISCUSSION

We addressed the topic of PKT in Egypt, because there is a question that whether the reported incidence of PLDKT correlates with the international values. Because this question may entail addressing the barriers and the promoting strategies of PLDKT, we performed this retrospective study to assess the outcomes of patients accessed KT at our center. In addition, review of PLDKT publications coming from Egypt was carried out in the context of the international literature, either as specific studies for PLDKT within LDKT cohorts or as combined LDKT and deceased donor KT researches. There is significant variability in the rates of PKT all over the world. In most studies, the proportions of PLDKT are higher than those of PKT in deceased donor KT. Most of these studies showed significantly higher incidences in adults and pediatrics. However, because the total percentages of LDKT are lower than those of KT from deceased donors, the frequency of PKT from deceased donors represented the majority of cases of PKT in some studies. However, relative to the total numbers of donor source, the percentages of PLDKT of total LDKTs are steadily higher than those of PKT from the total deceased donor KTs (Table 6).

In Egypt, there is an obvious lack of research on PKT represented by the small number of studies that was found in this topic[12-16]. These studies were mostly retrospective and presented as few centers' experiences or small cohorts of patients. Hence, the volume of research on PLDKT is relatively small, referring to that PKT does not seem to be in the focus of research. PLDKT has just been mentioned as a category within the total cohorts of KT from centers with well-established KT programs[13,17]. On the other hand, a few studies were specifically conducted to study PLDKT outcomes in comparison to CLDKT[9,12]. This may be a part of the lack in the international literature, which has a slowly propagating body of research on PKT[33,38]. Currently, the literature refers to some sort of practical negligence of PKT in many forms, including disparities in access to PKT among the waitlisted patients. In a study from the United States, relative to the rates of White (38%) and Black (31%) patients on the waiting list, there was a significant difference between the rates of White (65%) and Black (17%) patients who had PKT in 2019[1]. Also, there is a substantially lower rates of PAKT among certain demographic groups that may face challenges in engaging with complex health care systems. Patients with low levels of education and those with physician-dependent choice of KT are other groups with disparities in the access to PKT. Inequities in access to KT require substantial efforts and multiple remedies[1]. Unfortunately, there is no studies have been conducted in Egypt to measure the rates of access to PLDKT so far.

**Table 3** A comparison of the variables affecting the achievement ( $n = 59$ ) and non-achievement ( $n = 245$ ) of kidney transplantation in our center,  $n$  (%)

Variables	Achievement, $n = 59$	Non-achievement, $n = 245$	$P$ value
Age in yr, mean $\pm$ SD (range)	29 $\pm$ 9.9 (13-57)	32.8 $\pm$ 11.9 (12-66)	0.034
Sex			
Male	56 (94.9)	179 (73.1)	< 0.001
Female	3 (5.1)	66 (26.9)	
Dialysis status			
Preemptive access	4 (6.8)	28 (11.4)	0.354
On regular dialysis	55 (93.2)	217 (88.6)	
Primary kidney disease			
Unknown causes	41 (69.5)	202 (82.4)	0.008
Systemic diseases	3 (5.1)	18 (7.4)	
Renal diseases	15 (25.4)	25 (10.2)	
Number of potential donors per patient <sup>1</sup>			
Donor unavailability	0 (0)	44 (18)	0.003
One donor	43 (72.9)	161 (65.7)	
Two donors	13 (22)	31 (12.6)	
Three donors	3 (5.1)	9 (3.7)	
Outcome of donor evaluation <sup>1</sup>			
Accepted	48 (81.4)	51 (32.9)	< 0.001
Excluded	0 (0)	100 (64.5)	
Excluded and accepted	11 (18.6)	4 (2.6)	
Number of not-evaluated donors per patient <sup>1</sup>			
One donor	4 (100)	51 (86.4)	> 0.999
Two donors	0 (0)	7 (11.9)	
Three donors	0 (0)	1 (1.7)	
Chronological order of accepted donor <sup>1</sup>	$n = 59$	$n = 55$	
First	48 (81.4)	49 (89.1)	0.596
Second	8 (13.6)	4 (7.3)	
Third	3 (5.1)	2 (3.6)	
Age of accepted donors, mean $\pm$ SD (range)	40.2 $\pm$ 10.9 (21-60)	40.5 $\pm$ 9.5 (26-58)	0.937
Degree of relatedness of accepted donors <sup>1</sup>			
First	34 (57.6)	26 (47.3)	0.339
Second	20 (33.9)	25 (45.4)	
Third	3 (5.1)	4 (7.3)	
Unrelated	2 (3.4)	0 (0)	
Sex of accepted donor <sup>1</sup>			
Male	20 (33.9)	21 (38.2)	0.779
Female	39 (66.1)	34 (61.8)	
Number of excluded donors per patient <sup>1</sup>	$n = 11$	$n = 102$	
One donor	8 (72.7)	82 (80.4)	0.572
Two donors	3 (27.3)	17 (16.7)	

Three donors	0 (0)	3 (2.9)	
Main causes of donor exclusion <sup>1</sup>	<i>n</i> = 9	<i>n</i> = 100	
Medical causes	5 (55.6)	47 (47)	0.462
Immunologic mismatches	2 (22.2)	39 (39)	
Combined medical and immunologic causes	2 (22.2)	14 (14)	

<sup>1</sup>The values and percentages of the donors are not complementary to the total number of patients, because there were multiple donors for 56 patients who had overlapping outcomes of evaluation and fate.

SD: Standard deviation.

**Table 4 Multivariate logistic regression analysis of the variables influencing the achievement of kidney transplantation in our center**

Variables	Modality	Odds ratio	P value
Age	Younger <i>vs</i> older	0.97 (0.94-0.997)	0.031
Sex	Men <i>vs</i> women	0.14 (0.04-0.46)	0.001
Dialysis status	Preemptive <i>vs</i> on dialysis	0.31 (0.09-1.1)	0.065
Primary kidney disease	Known <i>vs</i> unknown	3.24 (1.5-6.9)	0.002
Number of potential donors	One <i>vs</i> multiple	0.81 (0.42-1.57)	0.529

The current study showed that PAKT represented only 10.5% of patients who were referred to KT in our center.

From the reviewed literature, the reported incidence of PLDKT in the different Egyptian KT centers was relatively lower than the international values (Tables 5 and 6). The range was 5%-6% of the total KTs that were performed in these centers[12,13]. However, the incidence was higher, when PLDKT was studied in a certain category of population, such as pediatrics with low-body weight[16,17]. Similarly, the rate of PLDKT was 5.1% in the current study. However, these values are still significantly lower than the values reported in the international literature (Table 6).

Patients with PAKT may have high education levels, payment resources, married status, residence near to KT centers, and younger age than those with CAKT. Unknown primary diseases and glomerulonephritis seemed to be the most common categories of primary kidney disease in adults[9,12,21]. Among pediatrics, reflux nephropathies, nephrotic syndromes, and congenital anomalies are the commonest primary diseases[15,16]. In addition, PLDKT patients had a lower likelihood of testing positive for hepatic viruses and receiving a blood transfusion than the CLDKT patients[12]. Of the 304 patients who accessed LDKT in our center, only 32 patients had PAKT. In turn, only 3 patients succeeded in having PLDKT and they included 2 children and 1 adult patient. They had congenital or hereditary diseases as primary causes of ESRD and the donors were unrelated donor in one case and mothers in the other 2 cases.

A large retrospective study from Mansoura Urology and Nephrology Center studied the course and outcomes of PLDKT and reported an incidence of 6.4%. In addition, it showed that there was only a significant difference in the percentages of patients who died with functioning grafts due to cardiovascular disorders and respiratory infections. The former cause was higher in PLDKT, while the latter was higher in CLDKT[12]. In a smaller prospective comparative study, we found that the incidence of acute graft rejection was significantly higher among early LDKT (ELDKT) patients than in PLDKT patients. However, the incidence of lymphoceles was significantly higher in PLDKT patients than in patients receiving ELDKT[9]. In the current study, the rates of non-candidacy and death during preparation to KT were lower in patients with PAKT (0%) than in patients with CAKT (10.7% and 35.7%, respectively). These rates may be because patients in the former group were healthier than those in the latter group.

The previous characteristic may be a surrogate of the concerns raised about the proposed effect of the lead-time bias on the advantaged outcomes of PLDKT. However, there may be a different perspective, regarding this postulation. We hypothesized that the proposed effects are a mere component of the strategy of PKT. This could simply be explained by considering the PKT and non-PKT as consecutive rather than parallel processes along the course of ESRD. PKT is an early step in the management of ESRD. So, the time factor should be considered a promotor rather than a confounder to PKT process. On the other hand, the idea of removal of the lead-time bias means discarding the spirit of the entire process of PKT[8]. The best support of this perspective is studying the outcomes of KT relative to the time-point at which KT is performed. Goldfarb-Rumyantzev *et al*[39] designed a study based on this idea and it revealed significant survival advantages when KT was performed before 180 d of dialysis.

**Table 5 Preemptive living donor kidney transplantation in publications from Egypt**

Ref.	Publishing place	Settings	Type	Aim	Scope relative to PLDKT	Target age group	Outcomes relative to ELDKT/ CLDKT	Number of patients; PLDKT/Total (Percentage of PLDKT)
El-Agroudy <i>et al</i> [12]	<i>Transplantation</i>	Mansoura University	Retrospective comparative	Compare outcomes of CLDKT & PLDKT	Specific	Mixed	Comparable, except in death with functioning graft was due to CVD in PLDKT <i>vs</i> respiratory infections in CLDKT	82/1279 (6.4%)
Bakr and Ghoneim[14]	<i>Saudi J Kidney Dis Transpl</i>	Mansoura University	Retrospective series	Present experience in KT	General	Mixed	Overall graft survival rates were 76% and 52% at five and 10-yr, respectively	82/1690 (4.9%)
El-Husseini <i>et al</i> [15]	<i>Pediatr Nephrol</i>	Mansoura University	Retrospective series	Evaluate outcomes of pediatric LDKT	General	Pediatrics	5-yr graft survival was 73.6%	51/216 (23%)
Mosaad <i>et al</i> [16]	<i>Dial Transpl</i>	Mansoura University	Retrospective series	Study LDKT survival in low-weight children	General	Pediatrics	PLDKT might provide better graft survival	9/63 (14.3%)
Saadi <i>et al</i> [13]	<i>Egyptian J Int Med</i>	Cairo University	Retrospective series	Identify KT Epidemiology in Cairo University hospitals	General	Mixed	Most of patients and donors were males, mostly as LDKT	14/282 (5%)
<sup>1</sup> Gadelkareem <i>et al</i> [9]	<i>Afr J Urol</i>	Assiut University	Prospective comparative	Compare short term outcomes of ELDKT & PLDKT	Specific	Adults	Comparable, except AR higher in ELDKT; Lymphocele incidence was higher in PLDKT	PLDKT 30/45; ELDKT 15/45
Gadelkareem <i>et al</i> [8]	<i>Exp Tech Urol Nephrol</i>	Assiut University	Opinion	Suppose that lead time should not be a bias effect in PKT	Specific	Mixed	Lead time is a mere character of PKT rather than a bias	NA
Fadel <i>et al</i> [17]	<i>Pediatr Transpl</i>	Cairo University	Retrospective series	Present experience in pediatric KT	General	Pediatrics	Timely referral and parent education were recommended	PLDKT 11/148 (7%); ELDKT 59/148 (40%)
Index study	<i>World J Nephrol</i>	Assiut University	Retrospective series	Present experience	Specific	Mixed	Urological causes are main contributor	PLDKT 3/59 (5.1%)

<sup>1</sup>Early living donor kidney transplantation was defined as receiving kidney transplantation within 6 mo from starting regular dialysis.

AR: Acute rejection; CLDKT: Conventional living donor kidney transplantation; CVD: Cardiovascular disease; ELDKT: Early living donor kidney transplantation; KT: Kidney transplantation; LDKT: Living donor kidney transplantation; N/A: Not applicable; PKT: Preemptive kidney transplantation; PLDKT: Preemptive living donor kidney transplantation.

Internationally, many articles have addressed the barriers of PKT. The unavailability of a suitable, willing donor is a major confounder to PLDKT[40-42]. In accordance, the current results revealed that younger age, male sex, and known primary kidney disease of patients accessing KT in our center were independent predictors of achievement of KT after preparation. However, the dialysis status (PAKT *vs* CAKT), number of potential donors, and their acceptance/exclusion rates were not significantly associated with the achievement of KT. The non-significant effect of PAKT may be attributed to the delayed access of the patients with ESRD. Most of our patients with PAKT were in stage 5 CKD and a mean eGFR of  $12.8 \pm 4.8$  mL/min/1.73 m<sup>2</sup>, when they first presented to our clinic. This value of eGFR is comparable to the reported values that allow successful PLDKT[33,43], but these patients were not prepared or waitlisted before presentation to the KT unit. Hence, they needed long duration for preparation, which might be, with donor exclusion, the causes of missing the chance of PLDKT. In addition, the delayed access might be attributed to absence of a well-configured waitlisting programs in our country to refer and prepare patients at the suitable stages of ESRD. On the other hand, there are many underlying primary renal diseases that may predispose to a very late presentation of a significant proportion of patients, such as the status of pending dialysis at first discovery of their ESRD[44].

Problems of unavailability of a well-integrated healthcare system that facilitates early detection of CKD patients and timely referral to KT centers should be practically considered. Paradoxically and despite the observable social fear of ESRD, which may progress up to a disease phobia in developing countries[45], there are many patient-related factors that influence early diagnosis and management of

**Table 6** Frequency of preemptive living donor kidney transplantation in publications from other countries/registries, *n* (%)

Ref.	Countryand/or Registry	Total KT Number	PKT	LDKT number (Percentage of PLDKT)	PKT per donor type	
					LD	DD
Migliori <i>et al</i> [19]	United States	1742	132 (7.6%)	1056 (9.1)	96 (73)	36 (27)
Berthoux <i>et al</i> [20]	ERA-EDTA	35348	2545 (7.2)	1097 (73.3)	804 (31.6)	1741 (68.4)
Asderakis <i>et al</i> [21]	United Kingdom	1463	161 (11)	118 (19.5)	23 (14)	138 (86)
Papalois <i>et al</i> [22]	United States	1849	385 (20.8)	1074 (29.1)	313 (81.3)	72 (18.7)
<sup>1</sup> Mange <i>et al</i> [23]	United States; USRDS	8489	1819 (21.4)	1819 (21.4)	1819 (100)	NA
Kasiske <i>et al</i> [24]	United States; UNOS	38836	5126 (13.2)	13078 (24)	3145 (61.4)	1981 (38.6)
Gill <i>et al</i> [25]	Canada; CORR	40963	5996 (14.6)	11290 (26.6)	2999 (50.5)	2967 (49.5)
Ashby <i>et al</i> [26]	United States; OPTN/SRTR	102331	17885 (17.5)	44033 (26.3)	11601 (65)	6284 (35)
<sup>1</sup> Ishikawa <i>et al</i> [27]	Japan; JRTR	834	112 (13.4)	834 (13.4)	112 (100)	NA
<sup>1</sup> Milton <i>et al</i> [28]	ANZDATA	2603	578 (22)	578 (22)	578 (100)	NA
<sup>1</sup> Yoo <i>et al</i> [29]	Korea	499	81 (16.2)	499 (16.2)	81 (100)	NA
Gore <i>et al</i> [30]	United States; UNOS	41090	11026 (26.8)	15940 (39.4)	6282 (57)	4744 (43)
Witczak <i>et al</i> [31]	Norway	3400	809 (24)	1415 (36.3)	514 (64)	295 (36)
<sup>2</sup> Kramer <i>et al</i> [32]	ERA-EDTA	1829	444 (21.2)	1073 (11.5)	123 (72)	321 (28)
Grams <i>et al</i> [33]	United States; UNOS	152731	19471 (12.8)	NA	11554 (59)	7917 (41)
<sup>1</sup> Grace <i>et al</i> [34]	ANZDATA	4105	660 (16.1)	2058 (16.1)	660 (100)	NA
<sup>2</sup> Patzer <i>et al</i> [35]	United States; USRDS	5774	1117 (19.3)	2598 (28.8)	747 (67)	370 (33)
Jay <i>et al</i> [2]	United States; UNOS	141254	24609 (17)	46373 (31)	14503 (59)	10106 (41)
Prezelin-Reydit <i>et al</i> [36]	France; REIN	22345	3112 (14)	2031 (34)	690 (22.2)	2422 (77.8)
<sup>1</sup> Kim <i>et al</i> [37]	South Korea	1984	429 (21.6)	1984 (21.6)	429 (100)	NA
<sup>2</sup> Prezelin-Reydit <i>et al</i> [38]	France; REIN	1911	380 (19.8)	240 (37.5)	90 (23.7)	290 (76.3)

<sup>1</sup>Studies included only living donor kidney transplantation.<sup>2</sup>Studies included only pediatric kidney transplantation.

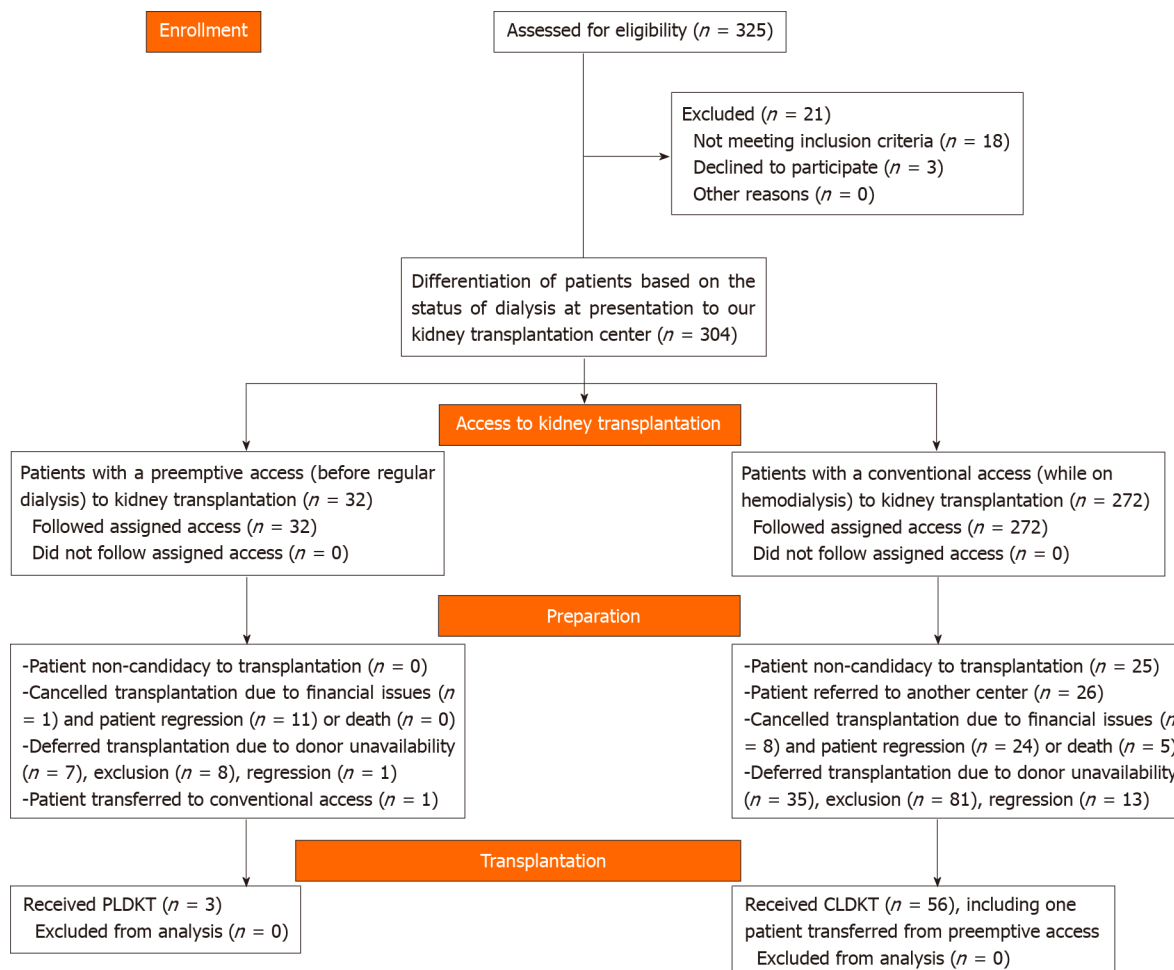
ANZDATA: Australia and New Zealand Dialysis and Transplant Registry; CORR: Canadian Organ Replacement Registry; DD: Deceased donor; ERA-EDTA: European Renal Association-European Dialysis and Transplant Association; JRTR: Japanese Renal Transplant Registry; LD: Living donor; LDKT: Living donor kidney transplantation; PKT: Preemptive kidney transplantation; PLDKT: Preemptive living donor kidney transplantation; N/A: Not applicable; OPTN/SRTR: Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients; REIN: Renal Epidemiology and Information Network; UNOS: United Network for Organ Sharing; USRDS: United State Renal Data System.

CKD patients such as the cultural and health illiteracies[44]. As a developing country, the healthcare authorities in Egypt have a large burden of challenges which seem hard to be overcome due to factors such as low per-capita income and slowly progressing corrections of the healthcare systems[15]. Also, the ethical problems that have been raised about KT practice in Egypt represent another major confounder to correction[46]. However, the recent policies in the Egyptian national healthcare system seem to be promising as a mass modification to overcome these problems, including the new national health insurance coverage and national KT programs.

The limitations of the current study included the small number of patients who had PLDKT, which made us unable to perform statistical analyses for the independent factors of failure of most patients with PAKT to achieve PLDKT. However, this is the first study from Egypt to address this very viable topic at a national review basis. Hence, it may unmask the vague situation of PLDKT in Egypt by configuring a step forward in building more integrated KT systems.

Based on relevant literature review, we may recommend implementation of different strategies to promote PLDKT in Egypt. Encouragement of LKD is the main strategy that should be extensively studied, because our national KT program is currently devoted to LDKT only. Minimally-invasive approaches such as laparoscopic living donor nephrectomy should be introduced to all centers of KT. Also, the regulations of LKD should be organized under a well-configured national donation program,





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**Figure 1** Flowchart of patients who accessed our center seeking living donor kidney transplantation. Relative to the status of dialysis at access, this chart shows the steps through which the patients and their potential donors were evaluated to achieve kidney transplantation. CLDKT: Conventional living donor kidney transplantation; PLDKT: Preemptive living donor kidney transplantation.

including donor exchange programs. Furthermore, promotion of healthcare facilities of early detection of CKD and education of the contributors of PLDKT process are crucial strategies for this topic. The latter includes the education of the physicians (representing the moderator of the process), ESRD patients (representing the key start of the process), and publics (representing the source of the potential donors) about the benefits of PKT.

## CONCLUSION

Patients with PAKT may have significant differences from those with CAKT regarding age, sex, primary kidney disease, and number of potential donors at presentation to a KT center. A primary kidney disease diagnosis is an independent factor of achievement of LDKT. In addition, older age and female sex are independent predictors of non-achievement of LDKT. On the other hand, unavailability, regression, and exclusion of LDs and patient regression when reach dialysis may hinder the achievement of PLDKT in patients with PAKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The current literature review may refer to that PLDKT has comparable or slightly better outcomes than those of CLDKT. Hence, PLDKT is recommended as the first choice for each candidate patient. In Egypt, PLDKT may have similar barriers to those presented elsewhere in the literature, including the shortage of donors, delayed presentation of patients and socioeconomic factors. As a result, the rate of PLDKT is still low in Egypt, warranting implementation of many strategies to promote PLDKT. They include encouraging LKD, introduction of minimally-invasive living donor nephrectomy, configuring a specific program for LKD, and education of the physicians, patients and publics about the benefits of PKT.



## ARTICLE HIGHLIGHTS

**Research background**

Despite its low rates, preemptive living donor kidney transplantation (PLDKT) is recommended as the optimal treatment for end-stage renal disease. However, its rate is still lower than the expected rates worldwide.

**Research motivation**

Promotion of the rate of PLDKT seems to be a modifiable variable for improvement of the total outcomes of KT.

**Research objectives**

To assess the rate of achievement of PLDKT among patients accessing KT in our center and to review the status of PLDKT in Egypt in the context of the international literature.

**Research methods**

We performed a retrospective review of the records of patients who accessed KT in our center from November 2015 to November 2022. The demographic and clinical characteristics of the patients and their potential donors were reviewed. Also, the literature was reviewed for PLDKT status in Egypt.

**Research results**

Of 304 patients accessed KT, 32 patients (10.5%) had preemptive access to KT (PAKT). The means of age and estimated glomerular filtration rate were  $31.7 \pm 13$  years and  $12.8 \pm 3.5$  mL/min/1.73 m<sup>2</sup>, respectively. Fifty-nine patients had KT, including three PLDKTs only (5.1% of the total KTs and 9.4% of PAKT). Twenty-nine patients (90.6%) failed to receive PLDKT due to donor unavailability (25%), exclusion (28.6%), regression from donation (3.6%), and patient regression on starting dialysis (39.3%). In multivariate analysis, known primary kidney disease ( $P = 0.002$ ), patient age ( $P = 0.031$ ) and sex ( $P = 0.001$ ) were independent predictors of achievement of KT in our center. However, PAKT was not significantly ( $P = 0.065$ ) associated with the achievement of KT. Review of the literature revealed lower rates of PLDKT in Egypt, including the current results, than the internationally reported rates.

**Research conclusions**

Patient age, sex, and primary kidney disease are independent predictors of achieving LDKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The main causes of non-achievement of PLDKT were patient regression on starting regular dialysis and donor unavailability or exclusion.

**Research perspectives**

Studying the factors that may promote the early access of ESRD patients to KT may improve the rates of PLDKT. This latter strategy may improve the whole outcomes of the process of KT, including avoidance of the inconveniences of dialysis and improvement of the graft and patient survival rates.

## FOOTNOTES

**Author contributions:** Gadelkareem RA, Abdelgawad AM, and Zarzour MA designed the research, collected the data, and wrote the paper; Reda A, Azoz NM, and Mohammed N contributed to the statistical analysis, literature review, writing and revision; Hammouda HM and Khalil M contributed to the literature review, writing, revision and supervision of the work; All authors approved the paper.

**Institutional review board statement:** This study has been approved in 2017 by the Medical Ethics Committee of the Faculty of Medicine, Assiut University, Egypt as a topic in a research project titled "Outcome of living donor kidney transplantation in Assiut Urology and Nephrology Hospital". The institutional review board number is 17200148.

**Informed consent statement:** This article is a retrospective study. Patients were not required to give informed consent to the study because the manipulated data were anonymous and were obtained after each patient agreed to treatment by consent.

**Conflict-of-interest statement:** The authors have no financial relationships to disclose.

**Data sharing statement:** The data supporting this study are available from the corresponding author on reasonable request.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was

prepared and revised according to the STROBE Statement – checklist of items.

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