Point-by-Point Response to the Reviewers Comments on Manuscript NO.: 82888, Retrospective Cohort Study

Preemptive Living Donor Kidney Transplantation: Access, Fate and Review of the Status in Egypt

Firstly, we would like to thank the Editors and Reviewers for their great efforts and time spent in reviewing this work to improve its quality.

Secondly, the responses to the instructions from the Editors are considered during preparation and submission of the revision files as per recommendations outlined in the first decision letter.

Thirdly, the responses to the reviewers' comments are presented as point-by-point report as following (Changes or corrections are performed in the text and they are highlighted in grey in the copied text after the responses below).

Responses to Reviewers Comments:

Responses to Comments of Reviewer #1:

Comment: "Scientific Quality: Grade B (Very good), Language Quality: Grade B (Minor language polishing), Conclusion: Accept (General priority)"

Response: Ok.

Comment: "Specific Comments to Authors: In this single center retrospective study from Egypt, the authors looked at the pattern/opportunity for pre emptive living donor kidney transplantatoion. Only 3 patients successfully underwent pre emptive living donor kidney transplantation. The authors disucssed the difficulty

in succesfully achieving pre emptive kidney transplantation and provided some recommendations to improve the success rates. Overall, the article is written well and will be useful information for the readers."

Response:

Thank you very much.

Responses to Comments of Reviewer #2:

Comment: "Scientific Quality: Grade D (Fair), Language Quality: Grade B (Minor language polishing), Conclusion: Major revision"

Response: Ok.

Comment: "Specific Comments to Authors: The manuscript faces in a retrospective study the experience of the authors with preemptive living kidney transplantation and in extenso faces with the same problem in the whole Egypt. The topic is interesting but it is restricted only the thge Egypt experience in a retrospective way and few number of transplantation."

Response: Yes. The number of transplantations is low, but the aim of the study was the evaluation of the access rate and not the transplantation rate (although the latter was a secondary outcome).

Comment: "Overall the study nothiong add to what already known."

Response: Kindly, the status of preemptive living donor kidney transplantation in Egypt has not been reviewed before and it is not known. Hence, reporting of this status and the rate of this type of transplant in Egypt provide information that may encourage this strategy of kidney transplantation. The information is cumulative and complementary to those from other countries.

Comment: "In addition the comparison with similar experience is extremely poor and the references are similarly poor."

Response: Yes. As the study was an original research, it was mainly devoted to presentation of the current result. Now, more information were added from the literature (Table 6) and references were strengthened by additions from studies from large transplant registries (References section, Pages 24-30).

Comment: The study should be rewriotten adding the frewal world experience and what has been made to overcome the limited number of such important type of kidney transplantation"

Response: Yes. Now, the study has been rewritten and more information added from international studies. Experiences of different regions and countries are now included in this article; Methods (Page 8, Paragraph 1), and Results (Page 9, Paragraph 1 and Table 6). The Discussion section has been enriched by correlations to these data at different sites (Discussion section; Pages 12-Paragraph 1 and 13-Paragraph 2). Also, the recommendations of the what have been made to overcome the limitations (Conclusion section, Page 18).

Comments of the Science editor:

Comment: "The manuscript has been peer-reviewed, and it' s ready for the first decision. Language Quality: Grade B (Minor language polishing), Scientific Quality: Grade C (Good)"

Response: Ok.

Response to comments of Company editor-in-chief:

Comment: "I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Nephrology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous

publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/."

Response:

Yes. all the recommendations and instructions have been addressed and corrected as per recommendation.

Name of Journal: World Journal of Nephrology

Manuscript Type: ORIGINAL ARTICLE

Retrospective cohort study

Preemptive Living Donor Kidney Transplantation: Access, Fate and Review of the Status in Egypt

Gadelkareem RA, et al. Preemptive access to kidney transplantation

Rabea A Gadelkareem, Amr M Abdelgawad, Ahmed Reda, Nashwa M Azoz, Mohammed A Zarzour, Nasreldin Mohammed, Hisham M Hammouda, Mahmoud Khalil

Rabea A Gadelkareem (ORCID: 0000-0003-4403-2859), **Amr M Abdelgawad (**ORCID: 0000-0002-4336-1573**), Ahmed Reda (**ORCID: 0000-0003-3699-5735**), Mohammed A Zarzour (**ORCID: 0000-0003-1449-6118**), Nasreldin Mohammed (**ORCID: 0000-0002-0232-9497**), Hisham M Hammouda (**ORCID: 0000-0003-2682-3876**), Mahmoud Khalil (**ORCID: 0000-0002-2564-5476**),** Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Assiut, Egypt.

Nashwa M Azoz (ORCID: 0000-0002-8455-1920), Department of Internal Medicine, Assiut University Hospital, Faculty of Medicine, Assiut University, Assiut, Egypt**.**

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 statistical analysis, literature review, writing and revision and Hammouda HM and Khalil M contributed to literature review, writing, revision and supervision of the work. All authors approved the paper.

Supported by: None.

Corresponding author: Rabea Ahmed Gadelkareem, MD, (ORCID: 0000-0003-4403-2859) Associate Professor, Department of Urology, Assiut Urology and

Nephrology Hospital, Faculty of Medicine, Elgamaa Street, Assiut University, Assiut, Egypt. Postal code: 71515; Tel.: 0882080435; Fax: 0882080236; E-mail: rabeagad@aun.edu.eg

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 accessing kidney transplantation (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 during November 2015–November 2021. In addition, the PLDKT status in Egypt was reviewed relative to the literature.

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±13 years and 12.8±3.5 ml/min/1.73 m^2, respectively. Fifty-nine patients had KT, including 3 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 (21.4%). In multivariate analysis, known primary kidney disease (p=0.002), patient age (p=0.031) and gender (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, gender, 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.

Keywords: Access to kidney transplantation; Donor regression; Kidney transplantation; Living donors; Preemptive kidney transplantation; Transplantation

Core tip:

Patients with preemptive access to kidney transplantation (PAKT) may have significant differences from those with conventional access to kidney transplantation (CAKT), warranting more evaluation and studying. In the current study, the known primary kidney disease was an independent factor of achievement of living donor kidney transplantation (LDKT). In addition, the older

age and female gender were independent predictors of non-achievement of LDKT. On the other hand, unavailability, regression, and exclusion of living donors and patient regression on starting dialysis may prevent the 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 outcomes to 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 the reported rates from other countries, warranting implementation of effective strategies to promote PLDKT.

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). This definition may vary from a KT program to another, where patients who receive dialysis sessions sporadically or as conditioning pretransplantation sessions for no more than one week may be included in this definition[1-6]. The evolution of PKT was more than 30 years ago[7], where it passed through an insidious course and gained variably insufficient interests among the physicians and surgeons in 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 the 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 possible as can. This philosophy represents the natural course of management of most of diseases. However, it has generated debates along the different axes of KT, such as the proposed lead-time bias effect on the outcomes of PKT[8]. 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 wait-

listing are other effective contributors to PKT. Hence, they are fundamental issues in PKT literature[1, 11]. However, they have mostly been ignored in researches coming from Egypt, where only LDKT is performed in adults[9,12-14] and pediatrics[15-17]. We aimed to assess the percentage of patients with PAKT and their fate, regarding the receipt of preemptive LDKT (PLDKT).

MATERIALS AND METHODS

Study design:

A retrospective review of the electronic and manual records of patients with ESRD who sought LDKT in our center during November 2015–November 2021. The study included both patients with PAKT which was defined as the presentation of a patient with CKD-stage 4 or 5 for KT prior to the start regular dialysis and those with a 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, gender, 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-EPI creatinine equation to estimate eGFR for patients with PAKT[18].

Also, a review of the literature was performed for assessment of PLDKT in KT researches coming 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 about the outcomes of LDKT at our center. The institutional review board number is 17200148/2017.

Statistical analysis: It was performed with EasyMedStat (version 3.21.4; www.easymedstat.com). Continuous variables were presented as mean ± standard deviation (SD) and range. However, categorical variables were presented as the number and percentage of each category. We created 2 groups (PAKT and CAKT) according to the status of dialysis at the time of access to transplantation. Normality and hetereoskedasticity of continuous data were assessed with White test (or with Shapiro-Wilk in multivariate analysis) and Levene's test, respectively. Continuous outcomes were compared with unpaired Student t-test, Welch t-test or Mann-Whitney U test according to data distribution. Categorical outcomes were compared with chi-squared or Fisher's exact test accordingly. A 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. A p-value <0.05 was considered statistically significant.

RESULTS

Between November 2015 and November 2021, 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 ± 10.5 (0.5–108) m. Both groups were compared for the demographic and clinical characteristics (Table 1). Follow-up after regression or exclusion decision varied from 3 months to 6 years.

In the group of PAKT, 29 patients (90.6%) failed to receive PLDKT due to donor original unavailability (25%), exclusion (28.6%), or regression (3.6%), or patient's regression from KT when started regular dialysis (39.3%) (Table 1). Hence, PLDKT was carried out in three patients only, representing 5.1% of the total KTs and 9.4% of patients with PAKT. One patient of these three patients died from complications of the corona virus disease-2019 (COVID-19), 6 months after KT. The other two patients were still living with a functioning graft for 68 and 12 months at the time of writing of this article (Table 2). The detailed characteristics of patients with PAKT are presented as individual patients (Table 2). The mean (range) age was 31.7 ± 12.9 (13–60) years. Most of patients present at stage 5 of CKD. The mean (range) for serum creatinine level and eGFR was 6 ±1.6 (3.2–9.8) mg/dl and 12.8 ±4.8 (7–28) ml/min/1.73 m^2, respectively.

In the current 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 the age (p=0.034), gender (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 gender (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).

Review of the literature for PLDKT in researches coming from Egypt revealed that only seven articles addressed PLDKT (Table 5). These articles came from four academic centers only, including 6 original researches and one opinion article. The percentage of PLDKT varied between 6.4% in adults and 23% in pediatrics. No articles addressed the PAKT or wait-listing. The reported patient and graft survival rates were similar to those of the conventional LDKT (CLDKT) in the literature.

In addition, 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 received LDKT than in those who received deceased donor KT (Table 6). In 1987, Migliori et al. were the first to evaluate the effects and outcomes of PKT in a large study from the United States of America (USA), reporting a PKT rate of 7.6%[19]. They were followed by two European studies with variable rates[20,21]. Then, 5 studies presented data from registries from USA and Canada and reported higher PKT rates up to 21% of the total KTs and more than 29% of LDKTs[22-26]. In addition, 3 studies from Japan, Australia, and Korea presented PLDKT rates up to 22% in patients receiving LDKT[27-29]. In 2009, 2 studies of mixed LD and deceased donor KTs showed higher rates of PLDKT about 39%[30,31]. Between 2011 and 2016, 5 studies of pediatric and adult KT showed similar rates[2,32-35]. Through the last 3 years, many studies 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

researches for PLDKT within LDKT cohorts or as combined LDKT and deceased donor KT researches. There is a significant variability in the rates of PKT all over the world. In most of 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 DDKT, 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 deceased donors of total KT from deceased donors.

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 USA, 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. 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 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 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 contributor 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]. Out of 304 patients accessed LDKT in our center, only 32 patients had PAKT. In turn, only three patients succeeded to have PLDKT and they included two children and one 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 two 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, significantly higher among early LDKT (ELDKT) patients than the PLDKT patients. However, the incidence of lymphoceles was significantly higher in PLDKT patients than that 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 those in

patients with CAKT (10.7% and 35.7%, respectively). These rates may refer to that the 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 have 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 as 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 et al. designed a study based on this idea and it revealed significant survival advantages when KT was performed before 180 days of dialysis[39].

Internationally, many articles have been 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 the younger age, male gender 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 versus 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 ±4.8 ml/min/1.73 m^2, when they firstly 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 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 the availability of well-integrated healthcare system that facilitates early detection of CKD patients and timely referral to KT centers. 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 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 the 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.

Limitations of the current study included the small number of patients who had PLDKT that empowered the inability to perform statistical analyses for the independent factors of failure of most patients with PAKT to achieve PLDKT. However, it is the first study from Egypt that addressed 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.

On the bases of 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 still until now 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, 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.

CONCLUSIONS

Patients with PAKT may have significant differences from those with CAKT, regarding the age, gender, primary kidney disease, number of potential donors at presentation to KT center. The primary kidney disease diagnosis is an independent factor of achievement of LDKT. In addition, the older age and female gender are independent predictors of non-achievement of LDKT. On the other hand, unavailability, regression, and exclusion of living donors 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 outcomes with 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 kidney transplantation (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 literature.

Research methods

We performed a retrospective review of the records of patients who accessed KT in our center during November 2015–November 2021. The demographic and clinical characteristics of the patients and their potential donors were reviewed. Also, the literature review was performed 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±13

years and 12.8±3.5 ml/min/1.73 m^2, respectively. Fifty-nine patients had KT, including 3 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 (21.4%). In multivariate analysis, known primary kidney disease (p=0.002), patient age (p=0.031) and gender (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, gender, 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, it 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.

ACKNOWLEDGEMENTS

None.

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Figure legend

Figure 1 A flowchart of patients who accessed our center seeking for 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.

Figure 1

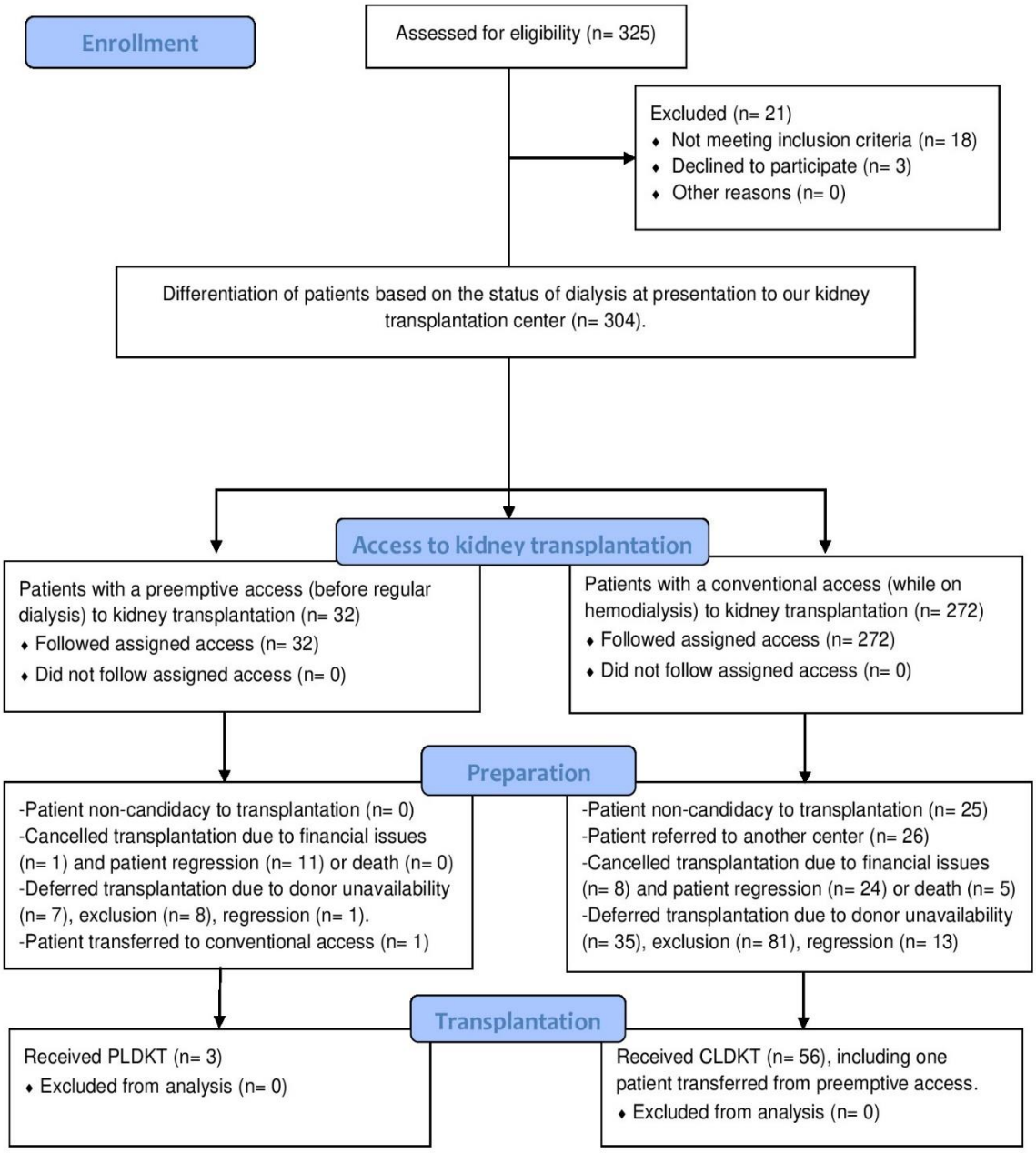
Enrollment
Assessed for eligibility (n= 325)
Excluded (n= 21)
♦ Not meeting inclusion criteria (n= 18)
♦ Declined to participate (n= 3)
♦ Other reasons (n= 0)
Differentiation of patients based on the status of dialysis at presentation to our kidney transplantation center (n= 304).
Access to kidney transplantation
Patients with a preemptive access (before regular dialysis) to kidney transplantation (n= 32)
♦ Followed assigned access (n= 32)
♦ Did not follow assigned access (n= 0)
Patients with a conventional access (while on hemodialysis) to kidney transplantation (n= 272)
♦ Followed assigned access (n= 272)
♦ Did not follow assigned access (n= 0)
Preparation
-Patient non-candidacy to transplantation (n= 0)
-Cancelled transplantation due to financial issues (n= 1) and patient regression (n= 11) or death (n= 0)
-Deferred transplantation due to donor unavailability (n= 7), exclusion (n= 8), regression (n= 1).
-Patient transferred to conventional access (n= 1)
-Patient non-candidacy to transplantation (n= 25)
-Patient referred to another center (n= 26)
-Cancelled transplantation due to financial issues (n= 8) and patient regression (n= 24) or death (n= 5)
-Deferred transplantation due to donor unavailability (n= 35), exclusion (n= 81), regression (n= 13)
Transplantation
Received PLDKT (n= 3)
♦ Excluded from analysis (n= 0)
Received CLDKT (n= 56), including one patient transferred from preemptive access.
♦ Excluded from analysis (n= 0)

Table 1 A comparison of the demographic and clinical characteristics of patients with preemptive access to kidney transplantation (PAKT) and those with conventional access to kidney transplantation (CAKT)

Variables	PAKT (n = 32)	CAKT (n = 272)	p-value
	Mean ± SD (range) or frequency (percentage)		
Age (year)	31.7 ± 13 (13–60)	32.1 ± 11.5 (12– 66)	0.677
Gender			
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 donorsF1			
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	n= 24	n= 236	
Patients with evaluated donors	n= 20	n= 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	n= 6	n= 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	n= 12	n= 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 (year)	38.1 ± 9 (25–53)	40.6 ± 10.4 (21–60)	0.390
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%)	
Gender 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	n= 5	n= 28	
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	n= 28	n= 191	
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%)	

F[1]: 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.

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

Case Number	Age (year)	Gender	No. of Potential donors (Relatedness)	Primary kidney disease	Serum creatinine (mg/dl)	Stage of CKD (eGFR) mL/min/1.73 m^2	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 VURD	4.7	4 (17)	Yes	NA	Living with a 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	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

Abbreviations: ADPCKD: autosomal dominant polycystic kidney disease, CMU: congenital megaureter, CKD: chronic kidney disease, CLDKT: conventional living donor kidney transplantation, COVID-19: coronavirus disease 2019, eGFR: estimated glomerular filtration rate, FSGS: focal segmental glomerulosclerosis, GN: glomerulonephritis, HD: hemodialysis, NA: not applicable, PLDKT: preemptive living donor kidney transplantation, PUV: posterior urethral valve, VURD: vesicoureteral reflux disease.

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

Variables	Achieved Transplantation (n = 59)	Non-achievement (n = 245)	p-Value
	Mean ± SD (range) or frequency (percentage)		
Age (year)	29 ± 9.9 (13–57)	32.8 ± 11.9 (12–66)	0.034
Gender			
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 F[1]			
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 F[1]			
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 F[1]			
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 F[1]	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	40.2 ± 10.9 (21–60)	40.5 ± 9.5 (26–58)	0.937
Degree of relatedness of accepted donors F[1]			
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%)	
Gender of accepted donor F[1]			
Male	20 (33.9%)	21 (38.2%)	0.779
Female	39 (66.1%)	34 (61.8%)	
Number of excluded donors per patient F[1]	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 F[1]	n= 9	n= 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%)

F[1]: 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.

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 versus older	0.97 [0.94–0.997]	0.031
Gender	Men versus women	0.14 [0.04–0.46]	0.001
Dialysis status	Preemptive versus on dialysis	0.31 [0.09–1.1]	0.065
Primary kidney disease	Known versus unknown	3.24 [1.5–6.9]	0.002
Number of potential donors	One versus multiple	0.81 [0.42–1.57]	0.529

Table 5 Preemptive living donor kidney transplantation (PLDKT) in publications from Egypt.

Study (Authors, year)	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 et al., 2004 [12]	Transplantation	Mansoura University	Retrospective comparative	Compare outcomes of CLDKT & PLDKT	Specific	Mixed	Comparable, except in death with functioning graft was due to CVD in PLDKT versus respiratory infections in CLDKT	82/1279 (6.4%)

Bakr and Ghoneim 2005 [14]	Saudi J Kidney Dis Transpl	Mansoura Univesity	Retrospective series	Present experience in KT	General	Mixed	Overall graft survival rates were 76% and 52% at five and 10-years, respectively	82/1,690 (4.9%)
El-Husseini et al., 2006 [15]	Pediatr Nephrol	Mansoura University	Retrospective series	Evaluate outcomes of pediatr LDKT	General	Pediatrics	5-yr graft survival was 73.6%	51/216 (23%)
Mosaad et al., 2012 [16]	Dial Transpl	Mansoura University	Retrospective series	Study LDKT survival in low-weight children	General	Pediatrics	PLDKT might provide better graft survival	9/63 (14.3%)
Saadi et al., 2017 [13]	Egyptian J Int Med	Cairo University	Retrospective series	Identify KT Epidemiology in Cairo	General	Mixed	Most of patients and donors were	14/282 (5%)

				University hospitals			males, mostly as LDKT	
Gadelkareem et al., 2017 [9] F[1]	Afr J Urol	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 et al., 2019 [8]	Exp Tech Urol	Assiut University	Opinion/ Perspective	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 et al., 2020 [17]	Pediatr Transpl	Cairo University	Retrospective series	Present experience	General	Pediatrics	Timely referral and parent	PLDKT 11/148 (7%)

				in pediatric KT			education were recommended	ELDKT 59/148 (40%)
Index study	World J Nephrol	Index University	Retrospective series	Present experience	Specific	Mixed	Urological causes are main contributor	PLDKT 3/59 (5.1%)

Abbreviations: 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, NA: Not applicable, PKT: Preemptive kidney transplantation, PLDKT: Preemptive living donor kidney transplantation.

F[1]: Early living donor kidney transplantation was defined as receiving kidney transplantation within 6 months from starting regular dialysis.

Table 6 Frequency of preemptive living donor kidney transplantation in publications from other countries/registries

Publication (Author, year)	Country &/or Registry	Total KT Number	PKT Number (Percentage)	LDKT number (Percentage of PLDKT)	Number (percentage) per donor type	
					LD	DD
Migliori et al. 1987[19]	USA	1,742	132 (7.6%)	1,056 (9.1%)	96 (73%)	36 (27%)
Berthoux et al. 1996[20]	ERA-EDTA	35,348	2,545 (7.2%)	1,097 (73.3%)	804 (31.6%)	1,741 (68.4%)
Asderakis et al. 1998[21]	UK	1,463	161 (11%)	118 (19.5%)	23 (14%)	138 (86%)
Papalois et al. 2000[22]	USA	1,849	385 (20.8%)	1,074 (29.1%)	313 (81.3%)	72 (18.7%)
Mange et al. 2001[23]F1	USA; USRDS	8,489	1,819 (21.4%)	1,819 (21.4%)	1,819 (100%)	NA
Kasiske et al. 2002[24]	USA; UNOS	38,836	5,126 (13.2%)	13,078 (24%)	3,145 (61.4%)	1,981 (38.6%)
Gill et al. 2004[25]	Canada; CORR	40,963	5,996 (14.6%)	11,290 (26.6%)	2,999 (50.5%)	2,967 (49.5%)
Ashby et al. 2007[26]	USA; OPTN/SRTR	102,331	17,885 (17.5%)	44,033 (26.3%)	11,601 (65%)	6,284 (35%)
Ishikawa et al. 2008[27]F1	Japan; JRTR	834	112 (13.4%)	834 (13.4%)	112 (100%)	NA
Milton et al. 2008[28]F1	ANZDATA	2,603	578 (22%)	578 (22%)	578 (100%)	NA

Yoo et al. 2009[29]F1	Korea	499	81 (16.2%)	499 (16.2%)	81 (100%)	NA
Gore et al. 2009[30]	USA; UNOS	41,090	11,026 (26.8%)	15,940 (39.4%)	6,282 (57%)	4,744 (43%)
Witczak et al. 2009[31]	Norway	3,400	809 (24%)	1,415 (36.3%)	514 (64%)	295 (36%)
Kramer et al. 2011[32]F2	ERA-EDTA	1,829	444 (21.2%)	1,073 (11.5%)	123 (72%)	321 (28%)
Grams et al. 2011[33]	USA; UNOS	152,731	19,471 (12.8%)	NA	11,554 (59%)	7,917 (41%)
Grace et al. 2013[34]F1	ANZDATA	4,105	660 (16.1%)	2,058 (16.1%)	660 (100%)	NA
Patzer et al. 2013[35]F2	USA; USRDS	5,774	1,117 (19.3%)	2,598 (28.8%)	747 (67%)	370 (33%)
Jay et al. 2016[2]	USA; UNOS	141,254	24,609 (17%)	46,373 (31%)	14,503 (59%)	10,106 (41%)
Prezelin-Reydit et al. 2019[36]	France; REIN	22,345	3,112 (14%)	2,031 (34%)	690 (22.2%)	2,422 (77.8%)
Kim et al., 2019[37]F1	South Korea	1,984	429 (21.6%)	1,984 (21.6%)	429 (100%)	NA
Prezelin-Reydit et al. 2022[38]F2	France; REIN	1,911	380 (19.8)	240 (37.5%)	90 (23.7%)	290 (76.3%)

Abbreviations: ANZDATA; Australia and New Zealand Dialysis and Transplant Registry, CORR; Canadian Organ Replacement Register, 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, NA; not accessible data/not applicable, OPTN/SRTR; Organ Procurement and Transplantation Network/ Scientific Registry of Transplant Recipients, REIN; Renal Epidemiology and Information Network, UK; United Kingdom, UNOS; United Network for Organ Sharing, USA; United States of America, USRDS; United State Renal Data System;.

F[1]: Studies include only pediatric age.

F[2]: Studies include only living donor kidney transplantation.