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NDT Perspectives

Does pre-emptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the Descartes Working Group and ERBP

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ABSTRACT

This position statement brings up guidance on pre-emptive kidney transplantation from living donors. The provided guidance is based on a systematic review of the literature.

Keywords: transplantation, living donation, pre-emptive, end stage renal failure, dialysis, guideline

FIRST STATEMENT

We recommend that programmes for pre-emptive kidney transplantation with living donor kidneys should be stimulated (1D)

Advice for clinical practice

Awareness programmes and early patient education on the possibility of pre-emptive living donation during the process of modality selection can enhance shared decision making when this becomes necessary.

RATIONALE

Why this question?

There is general consensus that, for suitable candidates, transplantation improves quality of life, and probably also longevity. However, due to organ shortage, there is a waiting time on dialysis for most patients. There is some concern that during this waiting time on dialysis, there is accumulation of co-morbidities associated with chronic renal failure and dialysis. Living donation can expand the available kidney donor pool, and creates the possibility for pre-emptive, i.e. before initiation of chronic dialysis, transplantation in a fair way. Pre-emptive transplantation has in addition the potential for the patient to avoid the need for creation of an arteriovenous fistula or peritoneal dialysis catheter surgery. Pre-emptive transplantation would also be cost-effective as the costs of dialysis are higher than those of the follow-up of transplanted patients. On the

other hand, there might be concerns that pre-emptive transplantation might result in an increased risk of graft loss from rejection because these patients do not present the immunosuppressive effects of uraemia and because the lack of experience with dialysis might negatively affect patient adherence. In addition, living donation, especially when pre-emptive, always raises the concern for the safety of the donor.

What did we find?

We used the PICO and search strategy as defined in Appendixes 1 and 2. We did not retrieve any randomized controlled trial comparing pre-emptive transplantation with post-dialysis transplantation. Only observational data, mainly coming from single centre or regional registries, are available.

We retrieved 29 retrospective observational cohort studies (26 published articles and 3 abstracts) performed after 1990 providing data on aspects of pre-emptive living donation [1–29] (Figure 1). We considered that older cohorts would be outdated and would not provide relevant data.

Twenty-two papers report mostly patients transplanted between 1990 and 2000, while seven report only on patients transplanted after 2000. Fifteen studies came from the USA, five from Europe and nine from other regions.

Twenty-one papers report on adult recipients and eight on paediatric recipients. In 13 articles, the donors were either living or deceased, in 10 they were only living donors and in 2 only deceased donors. For three studies, it was unclear what type of donors was actually included.

Data on patient survival, graft survival and acute rejection were provided in 19/29, 23/29 and 13/29, respectively, whereas risk for infection and malignancy was reported only in 2/29 (see Supplementary data, Appendix 3).

Patient survival, graft survival and acute rejection rate were better in pre-emptive versus after start of dialysis in 9 out of 19 (equivalent in 4), 13 out of 23 (equivalent in 2) and 10 out of 13 (equivalent in 2) papers reporting this outcome in adults, respectively. In children, patient survival was better in pre-emptive versus after start of dialysis in the only article reporting this outcome, graft survival was better [25, 26] in two out of four (equivalent in one [16] and worse in one [29]) and acute rejection rates were equivalent in two out of two papers reporting this outcome.

Some have shown a stepwise dose-dependent decrease in patient and graft survival with increasing duration of dialysis [6]. However, dialysis periods shorter than 1 year seem to have no significant impact on either patient or graft survival [13].

Occurrence of delayed graft function (DGF) was reported in four articles [4, 11, 12, 19]. The reported percentages of DGF varied between 2% [11] and 3.7% [12] with pre-emptive transplantation, versus 4% [11] and 9.7% [12] in patients transplanted after the start of dialysis.

All papers had a high risk for selection bias. This is visualized in the risk of bias grid (Figure 2) by the fact that it was uncertain whether pre-emptive patients were representative of the overall cohort, and whether non-pre-emptive patients were drawn from the same cohort. Further, there was uncertainty in most

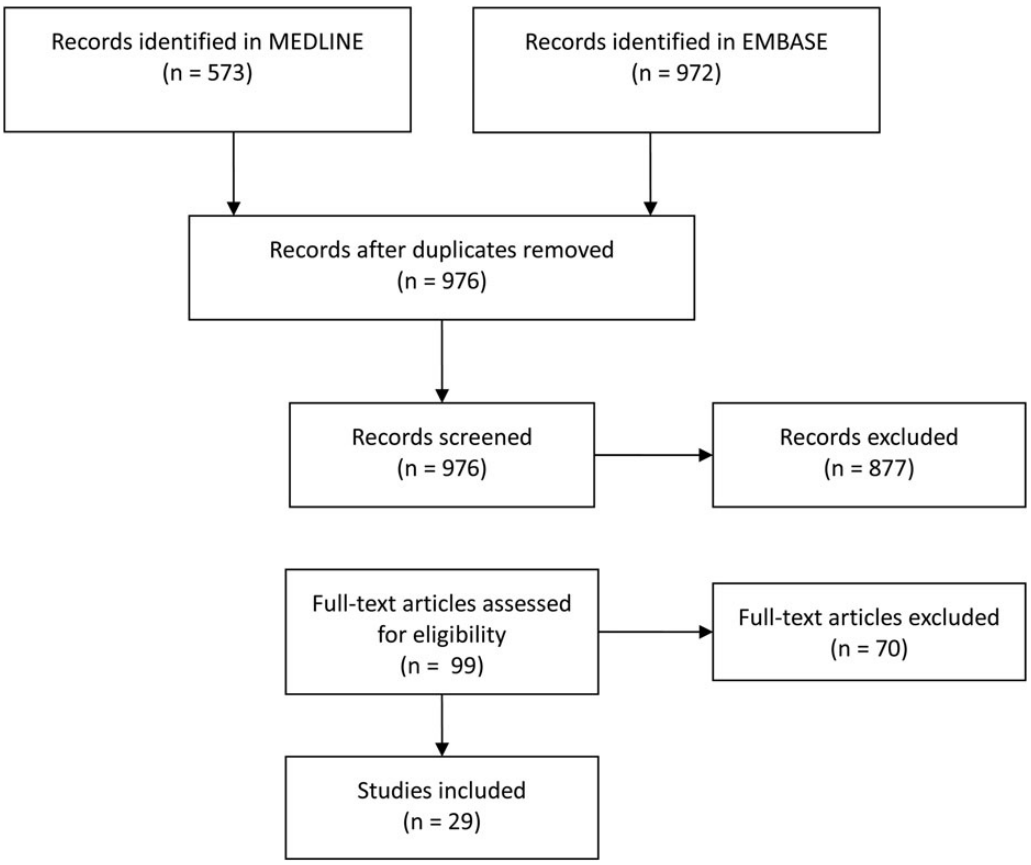

FIGURE 1: Flow diagram of study selection process.

Author year	Representative exposed cohort	non exposed cohort drawn from same community	adequate ascertainment of exposure	demonstration outcome of interest not present at start of study	adequate control for most crucial confounders	adequate control for additional confounders	adequate assessment of outcome	follow up long enough for outcomes to occur	adequate cohort follow-up
Jung 2010 [1]	0	0	+	+	-	-	+	+	+
Kasiske 2002 [2]	0	0	+	+	+	+	+	+	0
Katz 1991 [3]	0	0	+	+	-	-	-	+	+
Mange 2001 [4]	0	0	+	+	0	0	+	+	+
Meier-Kriesche 2000 [5]	0	0	+	+	0	0	+	+	+
Meier-Kriesche 2002 [6]	0	0	+	+	0	0	+	+	+
Milton 2008 [7]	0	0	+	+	0	0	+	+	+
Verbesey 2012 [8]	0	0	+	+	0	0	+	0	0
Wiseman 2013 [9]	0	0	+	+	-	-	+	+	+
Yoo 2009 [10]	0	0	+	+	-	-	+	+	+
Gill 2004 [11]	0	0	+	+	-	-	+	+	+
Innocenti 2007 [12]	0	0	+	+	0	0	0	+	-
Goldfarb-Rumyantzev 2005 [13]	0	0	+	+	+	0	+	+	+
Goldfarb-Rumyantzev 2006 [14]	0	0	+	+	-	+	+	+	+
Johnston 2013 [15]	0	0	+	+	+	+	+	+	+
Harada 2001 [16]	0	0	+	+	-	-	+	+	+
Heidotting 2011 [17]	0	0	+	+	-	-	+	+	+
Langlois 2000 [18]	0	0	+	+	+	-	+	+	+
Joo 2007 [19]	0	0	+	+	-	0	+	0	0
Ishikawa 2008 [20]	-	0	+	+	-	-	+	+	+
John 1998 [21]	-	0	+	+	-	-	+	+	+
Abou Ayache 2005 [22]	0	0	+	+	-	-	+	+	+
Becker 2006 [23]	0	0	+	+	+	+	+	+	+
Berthoux 1996 [24]	0	0	+	+	-	-	+	+	+
Butani 2011 [25]	0	0	+	+	-	-	0	+	+
Cransberg 2006 [26]	0	0	+	+	+	-	+	+	+
Cransberg 2000 [27]	0	0	+	+	-	-	+	+	+
Duzova 2009 [28]	0	0	+	+	-	-	-	+	+
Flom 1992 [29]	0	0	+	+	-	-	+	+	+

FIGURE 2: Risk of bias table.

studies as to whether essential and additional confounders were taken into account, also reflecting the potential presence of unadjusted imbalances between the pre-emptively and non-pre-emptively transplanted group.

How did we translate the evidence into the statement?

Several registry analyses (USRDS, ANZDATA and others) have reported better patient and graft survival in recipients with a pre-emptive transplantation when compared with those receiving a transplant after dialysis [2, 7, 13, 30].

However, these observational registry-based studies carry by nature important limitations. Pre-emptive kidney recipients are not necessarily representative of the overall transplanted patients, which should be kept in mind in the interpretation of the results. The risk of bias table indicates that there is a high risk that patients selected for pre-emptive transplantation differ from those who were not. For most studies, it was uncertain whether appropriate adjustments were done to correct for this potential imbalance.

First, they are more likely to receive a kidney from a living donor, a condition associated with better outcomes. Then, several studies have pointed out that socio-economic conditions of patients who receive pre-emptive transplantation are significantly better. They display higher education levels [31], are more wealthy [2] and have more frequently private health insurance [32]. US registries also reported ethnical differences

characterized by a higher proportion of Caucasians and non-Hispanics [2, 33] in the pre-emptive group. All these factors are known to be associated with better transplant outcomes that could partly explain the higher graft and patient survival after pre-emptive transplantation.

Furthermore, the patients who are pre-emptively registered on the waiting list have a better health condition. They present fewer cardiovascular comorbidities, have higher haemoglobin and albumin levels and were referred earlier to a nephrologist when compared with the patients placed on the waiting list after having started dialysis [34], which also contributes to improve the results after transplantation.

Even if we hypothesize that the improved patient and graft survival is biased because of confounding factors, we could not see any signals of worse outcomes with pre-emptive living donor kidney transplants. In particular, rates of acute rejections were generally lower with pre-emptive kidney transplantation, and there were no signals of non-adherence that were feared because of no prior experience with dialysis.

Remarkably, only two studies report long-term complications of transplantation, such as occurrence of malignancy (one study) or infection (two studies). It is thus not possible to gauge the impact of pre-emptive transplantation on these important long-term outcomes.

Taking into account that living donation expands the available donor pool, that pre-emptive transplantation seems to have beneficial effects and that eventual negative effects for the donor would not be different between pre-emptive versus non pre-emptive transplantation, the Descartes Working Group judged that at least patients should be informed about the option of pre-emptive living donation during pre-end-stage renal disease counselling.

However, it remains important that during the informing of the donor, sufficient attention is paid to explain potential short- and long-term risks for the donor.

What do the other guidelines state?

We did not retrieve any guideline body providing guidance on this topic.

AT WHAT GLOMERULAR FILTRATION RATE LEVELS COULD PATIENTS BE WAIT-LISTED FOR A PRE-EMPTIVE KIDNEY TRANSPLANTATION?

We recommend that pre-emptive transplantation is organized such that dialysis is avoided in a patient who otherwise would have to start it according to current guidelines (1A).

Why did we ask this question?

Previous guidelines recommended performing a pre-emptive kidney transplantation from a living donor when the glomerular filtration rate (GFR) was below 15 mL/min [35]. However, transplantation is associated with a small increased risk of death in the early weeks/months after the procedure. Furthermore, the intervention also puts the donor at a small but definite increased risk of complications, including death, after kidney harvesting. Therefore, pre-emptive transplantation must not be performed too early, as it may harm both donor and recipient without reason.

What did we find?

Only a limited number of studies have compared transplant outcomes when pre-emptive transplantation was performed at different levels of GFR. Neither patient nor graft survival was influenced by the level of pre-transplant GFR (>20, 15–20, 10–15 or <10 mL/min/1.73 m^2) [36–38].

How did we translate the evidence into the statement?

The optimal timing for pre-emptive Tx should be 'shortly or a few months before the need to initiate dialysis'. In line with the IDEAL study [39], this is when uraemic clinical symptoms or biochemical abnormalities supervene. This will usually happen when the GFR is between 7 and 10 mL/min [39]. Furthermore, pre-emptive transplantation should be performed only in recipients who have a renal disease that is definitely irreversible and clearly progressive. Beyond GFR, some further information on the speed of kidney function decline can be gained by considering parameters such as urine albumin/creatinine ratio and the levels of serum calcium, phosphorus, bicarbonate and serum albumin. These parameters have been computed into a 'kidney failure risk equation' (freely downloadable, http://www.qxmd.com/Kidney-Failure-Risk-Equation) that helps to predict when dialysis will be needed with a better accuracy than GFR alone [40]. However, it should be realized that predicting evolution of GFR in the individual patient can be cumbersome.

The timing of the pre-transplantation work-up of both donors and recipients should be done some weeks/months before the planned transplantation, according to centre practices.

The position statement stresses that pre-emptive Tx should be planned in order to avoid dialysis, and is not based on a fixed, pre-determined level of GFR but rather should take into account both clinical and biochemical evidences.

SUGGESTION FOR FUTURE RESEARCH

To set-up a quality registry with the aim to:

- compare the GFR at which patients are pre-emptively transplanted in different countries in Europe.
- measure the outcomes of these patients in terms of patient and graft survival, quality of life and adverse events (infection, cancer, major adverse cardiovascular events) and associate them with estimated glomerular filtration rate (eGFR) at pre-emptive transplantation register outcomes of their living donors in terms of mortality, QoL, major cardiovascular events and evolution of eGFR and albuminuria.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Jung GO, Moon JI, Kim JM *et al.* Can preemptive kidney transplantation guarantee longer graft survival in living-donor kidney transplantation? Single-center study. Transplant Proc 2010; 42: 766–774
2. Kasiske BL, Snyder JJ, Matas AJ *et al.* Preemptive kidney transplantation: the advantage and the advantaged. J Am Soc Nephrol 2002; 13: 1358–1364
3. Katz SM, Kerman RH, Golden D *et al.* Preemptive transplantation—an analysis of benefits and hazards in 85 cases. Transplantation 1991; 51: 351–355
4. Mange KC, Joffe MM, Feldman HI. Effect of the use or nonuse of long-term dialysis on the subsequent survival of renal transplants from living donors. N Engl J Med 2001; 344: 726–731
5. Meier-Kriesche HU, Port FK, Ojo AO *et al.* Effect of waiting time on renal transplant outcome. Kidney Int 2000; 58: 1311–1317
6. Meier-Kriesche H-U, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. Transplantation 2002; 74: 1377–1381
7. Milton CA, Russ GR, McDonald SP. Pre-emptive renal transplantation from living donors in Australia: effect on allograft and patient survival. Nephrol Carlton Vic 2008; 13: 535–540
8. Verbesey J, Nilubol C, Melancon K *et al.* Preemptive kidney transplant may not offer survival advantage in octogenarian transplant recipients. Am J Transplant 2012; 12: 488
9. Wiseman AC, Huang E, Kamgar M *et al.* The impact of pre-transplant dialysis on simultaneous pancreas-kidney versus living donor kidney transplant outcomes. Nephrol Dial Transplant 2013; 28: 1047–1058
10. Yoo SW, Kwon OJ, Kang CM. Preemptive living-donor renal transplantation: outcome and clinical advantages. Transplant Proc 2009; 41: 117–120
11. Gill JS, Tonelli M, Johnson N *et al.* Why do preemptive kidney transplant recipients have an allograft survival advantage? Transplantation 2004; 78: 873–879
12. Innocenti GR, Wadei HM, Prieto M *et al.* Preemptive living donor kidney transplantation: do the benefits extend to all recipients? Transplantation 2007; 83: 144–149
13. Goldfarb-Rumyantzev A, Hurdle JF, Scandling J *et al.* Duration of end-stage renal disease and kidney transplant outcome. Nephrol Dial Transplant 2005; 20: 167–175
14. Goldfarb-Rumyantzev AS, Hurdle JF, Baird BC *et al.* The role of pre-emptive re-transplant in graft and recipient outcome. Nephrol Dial Transplant 2006; 21: 1355–1364
15. Johnston O, Rose CL, Gill JS *et al.* Risks and benefits of preemptive second kidney transplantation. Transplantation 2013; 95: 705–710
16. Harada H, Seki T, Nonomura K *et al.* Pre-emptive renal transplantation in children. Int J Urol 2001; 8: 205–211
17. Heidotting N, Ahlenstiel T, Pape L. Living related donation leads to a decreased severity of arterial hypertension after pediatric kidney transplantation. Pediatr Transplant 2011; 15 (Suppl 1): 124
18. Langlois V, Geary D, Murray L *et al.* Polyuria and proteinuria in cystinosis have no impact on renal transplantation. A report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol 2000; 15: 7–10
19. Joo KW, Shin SJ, Lee SH *et al.* Preemptive transplantation and long-term outcome in living donor kidney transplantation, single-center experience. Transplant Proc 2007; 39: 3061–3064
20. Ishikawa N, Yagisawa T, Sakuma Y *et al.* Preemptive kidney transplantation of living related or unrelated donor-recipient combinations. Transplant Proc 2008; 40: 2294–2296
21. John AG, Rao M, Jacob CK. Preemptive live-related renal transplantation. Transplantation 1998; 66: 204–209
22. Abou Ayache R, Bridoux F, Pessione F *et al.* Preemptive renal transplantation in adults. Transplant Proc 2005; 37: 2817–2818
23. Becker BN, Rush SH, Dykstra DM *et al.* Preemptive transplantation for patients with diabetes-related kidney disease. Arch Intern Med 2006; 166: 44–48
24. Berthoux FC, Jones EH, Mehls O *et al.* Transplantation Report. 2: Preemptive renal transplantation in adults aged over 15 years. The EDTA-ERA Registry. European Dialysis and Transplant Association-European Renal Association. Nephrol Dial Transplant 1996; 11 (Suppl 1): 41–43
25. Butani L, Perez RV. Effect of pretransplant dialysis modality and duration on long-term outcomes of children receiving renal transplants. Transplantation 2011; 91: 447–451
26. Cransberg K, Smits JMA, Offner G *et al.* Kidney transplantation without prior dialysis in children: the Eurotransplant experience. Am J Transplant 2006; 6: 1858–1864
27. Cransberg K, van Gool JD, Davin C *et al.* Pediatric renal transplantation in the Netherlands. Pediatr Transplant 2000; 4: 72–81
28. Duzova A, Bilginer Y, Aki F *et al.* Preemptive renal transplantation in a mediterranean country. Pediatr Transplant 2009; 13 (Suppl 1): 82
29. Flom LS, Reisman EM, Donovan JM *et al.* Favorable experience with pre-emptive renal transplantation in children. Pediatr Nephrol 1992; 6: 258–261
30. Witczak BJ, Leivestad T, Line PD *et al.* Experience from an active pre-emptive kidney transplantation program—809 cases revisited. Transplantation 2009; 88: 672–677
31. Davis CL. Preemptive transplantation and the transplant first initiative. Curr Opin Nephrol Hypertens 2010; 19: 592–597
32. Grams ME, Chen BP-H, Coresh J *et al.* Preemptive deceased donor kidney transplantation: considerations of equity and utility. Clin J Am Soc Nephrol 2013; 8: 575–582
33. Weng FL, Mange KC. A comparison of persons who present for preemptive and nonpreemptive kidney transplantation. Am J Kidney Dis 2003; 42: 1050–1057
34. Kutner NG, Zhang R, Huang Y *et al.* Impact of race on predialysis discussions and kidney transplant preemptive wait-listing. Am J Nephrol 2012; 35: 305–311
35. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: long-term management

of the transplant recipient. IV.13 Analysis of patient and graft survival. Nephrol Dial Transplant 2002; 17 (Suppl 4): 60–67
36. Ishani A, Ibrahim HN, Gilbertson D *et al.* The impact of residual renal function on graft and patient survival rates in recipients of preemptive renal transplants. Am J Kidney Dis 2003; 42: 1275–1282
37. Akkina SK, Connaire JJ, Snyder JJ *et al.* Earlier is not necessarily better in preemptive kidney transplantation. Am J Transplant 2008; 8: 2071–2076
38. Grams ME, Massie AB, Coresh J *et al.* Trends in the timing of pre-emptive kidney transplantation. J Am Soc Nephrol 2011; 22: 1615–1620
39. Cooper BA, Branley P, Bulfone L *et al.* A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 2010; 363: 609–619
40. Tangri N, Stevens LA, Griffith J *et al.* A predictive model for progression of chronic kidney disease to kidney failure. JAMA 2011; 305: 1553–1559
41. Nagler EV, Webster AC, Bolignano D *et al.* European Renal Best Practice (ERBP) Guideline development methodology: towards the best possible guidelines. Nephrol Dial Transplant 2014; 29: 731–738
42. Higgins JPT, Altman DG, Gøtzsche PC *et al.* The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928
43. Wells GA, Shea B, Higgins JP *et al.* Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. Res Synth Methods 2013; 4: 63–77
44. Guyatt GH, Oxman AD, Kunz R *et al.* Going from evidence to recommendations. BMJ 2008; 336: 1049–1051

METHODS FOR GUIDANCE DEVELOPMENT

Composition of the guidance development group

Descartes and ERBP joined forces to develop this position statement on pre-emptive kidney transplantation. The guidance development group consisted of experts in kidney transplantation, adult and paediatric nephrology, who are all members of the Descartes group. ERBP provided support in guidance development and systematic review methodology. The systematic review that was carried out to inform this position statement complies with ERBP's guidance development methodology standards [41].

Framing of the questions

Two specific clinical questions were developed within the guidance development group:

(i) Does pre-emptive transplantation with a kidney from a living donor improves outcomes after transplantation?

(ii) At what GFR levels could patients be wait-listed for a pre-emptive kidney transplantation?

The clinical questions were translated into the PICOM format with pre-specification of the eligible target **P**opulation, **I**ntervention, **C**omparator, **O**utcome and study design **M**ethodology, and explicit inclusion criteria for study selection were defined (Appendix 1).

Literature search and study selection process

A search strategy with Boolean combinations of terms for 'kidney transplantation' and 'pre-emptive' was constructed (Appendix 2) and used to identify eligible studies in MEDLINE and EMBASE. Both databases were searched on 16 May 2013, results of both databases were combined and de-duplicated (Supplementary data, Appendix 3). Two guideline development group members performed screening by title and abstract independent from each other and assessed the full text of each potentially relevant study to determine eligibility for inclusion using the pre-defined inclusion criteria defined within the PICOM framework. Discrepancies were resolved by discussion within the group.

We included all study designs in humans with the minimum requirement of at least one patient in both treatment groups without any language restrictions that compared pre-emptive kidney transplantation with transplantation after dialysis treatment had been initiated. We excluded case reports, narrative review articles and editorials without primary data.

Data extraction and risk of bias assessment

Relevant information on design, conduct, characteristics of study participants, outcomes and risk of bias were collected from each included study in duplicate by two guideline development group members independently from each other using a standardized form. Risk of bias of the included studies was assessed using validated checklists, the Cochrane Risk of Bias tool for randomized controlled trials [42] and the Newcastle Ottawa scale for Cohort and Case–control studies [43]. Results of the data extraction of each individual study were then used to generate summary of findings tables per outcome across studies and for the risk of bias of each domain per study (Supplementary data, Appendix 3).

Formulating and grading recommendations

The guideline development group used the data extraction tables and summary of findings tables to formulate and grade the recommendations. We applied the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) methodology to grade the quality of the evidence and the strength of the recommendations [44].

Writing the rationale

Guideline development group members wrote the rationale according to a pre-specified format that outlines relevant background information on the topic, reviews the evidence and states how the evidence was translated into the statement.

APPENDIX 1

Clinical question structured in PICOM format.

Is preemptive kidney transplantation from a living donor compared to kidney transplantation from a living donor after initiation of dialysis treatment associated with improved outcomes?

Population	Adult and pediatric recipients of a kidney transplant from a living donor
Intervention	Preemptive kidney transplantation from a living donor
Comparator	Kidney transplant from a living donor after initiation of dialysis treatment

Outcomes	Patient survival, graft survival, acute rejection, infection, malignancy
Methods	Randomized controlled trials, cohort studies, case–control studies, minimum requirement is $n = 1$ in each group (intervention and comparator group)

APPENDIX 2

Search strategy for MEDLINE and EMBASE

(1) exp Kidney Transplantation/
(2) pre-emptive.tw.
(3) preemptive.tw.
(4) pre?mpti$.tw.
(5) or/2-4
(6) 1 and 5

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