

Peer Review File

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Reviewer A

The manuscript entitled “Comparison of in situ preservation techniques for kidneys from donors after cardiac death: a systematic review and meta-analysis.”, refers to the best method of kidney preservation when organs are procured form donors after circulation death.

Last decade has given us a lot of new insight into the organ storage techniques and conditions.

There is an ongoing discussion about the best preservation techniques when organs are procured. Transplantation of organs from donors after circulatory death (DCD) is connected with worse (but still acceptable) results as the transplant society has to deal with organ shortage.

As we face different organ quality (DBD, DCD, SCD, ECD, LD), it seems we should develop tailor made preservation techniques depending on donor type. It is very important to establish common recommendations for DCD kidney preservation. The systematic review and meta-analysis is an useful tool to answer the question which technique is the best.

Could you please refer to the questions below?

Comments:

- **Comment 1:** Title – “... donors after cardiac death ...” – the proper term is: donor after circulatory death (DCD). In the manuscript body authors used the proper term.

Reply 1: The concept of “Donation or Donor after Circulatory Death (DCD)” is a more precise term to define organ donors after circulatory arrest and has been adopted by the World Health Organization (WHO). Previously, it was referred to as donation after cardiac death or non-heartbeating organ donation.

Changes in the text: We have changed the title following the reviewers' suggestions. The correct title would be: “**Comparison of in situ preservation techniques for kidneys from donors after circulatory death: a systematic review and meta-analysis**” (see Page 1, line 1-2).

- **Comment 2:** In Abstract authors said: “... because of the additional benefit for liver preservation.” – there is no confirmation in the Results for this statement.

Reply 2: Although the use of in situ normothermic perfusion is a crucial aspect of DCD organ preservation and is now considered necessary by groups performing DCD liver transplantation to not only limit warm ischemia but also reverse ischemic injury, our systematic review and meta-analysis focused on kidney preservation.

Changes in the text: We have deleted this sentence in the Abstract (see Page 4, lines 4-5), but it has been remarked as an essential data in Discussion section (see Page 15, lines 2-3).

- **Comment 3:** Introduction:

o “Kidney transplantation is the best treatment for patients with end-stage renal disease, as it results in sustained improvement in quality of life compared with dialysis” – This is not only the matter of quality of life. Patients after kidney transplantation have better survival in comparison to dialysis population.

Reply 3: It has been sufficiently demonstrated that a successful kidney transplantation improves the quality of life and reduces the mortality risk for most patients when compared with remaining on dialysis.

Changes in the text: We added some data (see Page 4, lines 12-13). “Kidney transplantation is the best treatment for patients with end-stage renal disease, as it results in sustained improvement in quality of life compared with dialysis and increases life expectancy”

• **Comment 4:** Results:

o “DGF is an early complication after kidney transplantation with a negative impact on allograft outcomes.” – this sentence should not be in the results section (consider to move it to discussion)

Reply 4: This sentence has been used to introduce DGF outcome. However, it does not correspond to findings obtained in our study. It is better placed in the Discussion section because it properly contextualizes the findings.

Changes in the text: According to reviewers' recommendations, the sentence was moved to the Discussion section (see Page 16, lines 8-9).

o **Comment 5:** "Graft loss is identified as one of the critically important outcome domains in kidney transplantation for health professionals, along with mortality, graft function and chronic graft rejection(15)." – this sentence should not be in the results section (consider to move it to discussion)

Reply 5: This sentence has been used to introduce the outcome of graft loss. Nevertheless, it does not correspond to findings obtained in our study. It is better placed in the Discussion section because it properly contextualizes the findings.

Changes in the text: According to reviewers' recommendations, the sentence was moved to the Discussion section (see Page 17, lines 18-20).

• **Comment 6:** Discussion:

o In general authors did not refer much to the results section. In the discussion part more elaboration on findings is expected.

Reply 6: We have checked each subtopic in the Discussion section and we have stated if our results confirm or are in contrast with previous evidence.

Changes in the text: We added some data.

“Our meta-analysis revealed that grafts preserved using NRP could be superior to those preserved using other techniques regarding DGF rates (0.36, 95%CI 0.25-0.54), and no heterogeneity was found for the effect ($p = 0.37$; $I^2 = 14.32\%$) between groups. In contrast, PNF rate does not appear to be improved using this technique according to the pooled OR obtained from the meta-analysis (0.93, 95%CI 0.43-2.00).” (see Page 17, lines 2-6).

o **Comment 7:** “The findings from the few heterogeneous retrospective studies reported to date indicate that NRP offers benefits when compared with conventional in situ cold preservation. The results of a systematic review of the literature highlight the promising results of NRP compared to a super-rapid recovery procedure or in situ cooling, with reduced PNF or DGF rates.” - this does not come from the results. I would be more cautious in expression such thoughts.

Reply 7: We have re-written this paragraph to better express the results and conclusions of our systematic review and meta-analysis.

Changes in the text:

“The findings from the few heterogeneous retrospective studies reported to date indicate that NRP could offer benefits when compared with conventional in situ cold preservation. The results of a systematic review of the literature highlight the promising results of NRP compared to a super-rapid recovery procedure or in situ cooling, with reduced DGF rates. However, evidence is weak due to the heterogeneity of studies included and these results should thus be treated with caution” (see page 18, lines 1-6).

o **Comment 8:** Furthermore, ethical issues limit widespread acceptance and implementation of DCD transplantation.“ – this sentence is (maybe true) out of context and do not come from the analysis.

Reply 8: The ethical issues surrounding in situ preservation should be mentioned. However, following reviewers’ recommendations, it has been moved to Introduction section.

Changes in the text: According to reviewers’ recommendations, the sentence was moved to the Introduction section (see Page 6, lines 21-22) and Discussion section (see Page 25, lines 22-23).

• Conclusions:

o **Comment 9:** “The findings concerning in situ preservation techniques on the different graft outcomes suggest that PNF and DGF rates could be reduced by using NRP compared to other preservation techniques.” – the presented results did not support this statement.; according to the meta-analysis NRP reduces DGF only.

The outcome effect measure is expressed as OR. The 1 value means no difference. Looking at the pooled effect estimate, regarding PNF, the NRP (OR: 0.93, 95% CI: 0.43, 2) does not show a statistically significant effect favouring this technique. Regarding DGF (pooled OR: 0.36, 95% CI: 0.25, 0.54), the presented data suggest that rates of this outcome could be reduced by using NRP.

Changes in the text: We have modified the text to correct the mistake (see Page 18, line 13-15).

“The findings concerning in situ preservation techniques on the different graft outcomes suggest that DGF rates could be reduced by using NRP compared to other preservation techniques.”

- **Comment 10:** Could please point out the weak points of this study?

Reply 10: Limitations of our study have been identified.

Changes in the text: We added some data (see Page 18, lines 8-9).

“The small and scarce retrospective studies, together with the heterogeneous outcomes, are limitations to this study”.

Reviewer B

This report is a systematic review and meta-analysis of the effects of preservation techniques for kidneys from donors from cardiac death.

The topic was interesting.

The study’s methodology was correct, and the manuscript was well written.

I have the following comments for the authors’ consideration.

1. **Comment 1:** On page 13, line 10, the authors mentioned, “Kidney allografts preserved using in situ cooling had higher PNF rates than allografts preserved with NRP.” I felt that Group 3 in Figure 2 did not show it.

Reply 1: Figure 2 represents the forest plot of meta-analysis regarding PNF. Groups: 2 - NRP versus HRP, 3 - NRP versus ISC ,4 - NRP versus SRR, 5 - NRP versus TBC. The 1 value means no difference. Looking at the pooled effect estimate (group 3), regarding PNF, the NRP (OR: 0.73, 95% CI: 0.28, 1.94) does not show a statistically significant effect favouring this technique.

Changes in the text: The sentence has been re-written (see Page 13, lines 6-8).

“Kidney allografts preserved using in situ cooling had higher PNF rates than allografts preserved with NRP in the series of Del Rio et al. Nevertheless, the pooled OR does not show difference between the two groups.”

2. **Comment 2:** The authors should clarify the abbreviation of PNF, NRP, HRP, etc. in the footnote of Figure 1, 2 and 3

Reply 2: We previously defined abbreviations in the manuscript before we used them. Furthermore, they have been included in the footnote of figures and tables.

Changes in the text: Abbreviations have been included in the footnote of figures and tables.