Dear Editor,

On behalf of all Co-authors, I would like to sincerely thank you for considering our Minireview

entitled "**Robot-assisted kidney transplantation: is it getting ready for prime time?"** for publication in the World Journal of Transplantation, and for giving us the opportunity to submit a revised version of the paper.

We have carefully revised the manuscript taking into consideration all the points raised by the Reviewers, providing detailed explanations on all aspects of concerns.

We have checked the accuracy of the data provided in the manuscript, as appropriate.

We have put all our efforts to address the Reviewers' comments and improving the quality of the manuscript in the very best way.

Please find below a point-to-point reply to the Reviewers' comments.

Thanking you and the Reviewers very much for the time dedicated to our manuscript, and hoping to have met your expectations,

Kind Regards,

Corresponding Author:

Vincenzo Li Marzi, MD

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an article written to promote robot-assisted kidney transplantation in the deceased donation setting. The main idea behind this was presented as the ability to include marginal otherwise high-risk surgical patients to the recipient list by minimizing the surgical trauma. My criticisms are as follows:

1. ***This purpose can only be justified by truly including marginal recipients in the studies. On the contrary, the patients included in the studies are comparatively better, with higher preemptive status in the robotic arm and lower ASA scores.***

   We thank the Reviewer for this comment. We completely agree. As reported in the limitation of our study, the main problem remains the selection bias for this procedure. Despite all efforts, an international multicentre randomized trial is strongly needed to

provide high-quality evidence regarding the real clinical impact of robotic surgery in this field. We've highlighted this relevant issue in DISCUSSION OF THE EVIDENCE AND FUTURE PERSPECTIVES.

2. ***The literature is filled with evidence regarding the negative effects of prolonged cold and warm ischemia times. Some articles provide range and increased graft failure risk with every minute of added warm ischemia. How do authors explain that despite prolonged CIT and WIT, the graft outcomes are similar?***

   We thank the Reviewer for this comment, which allowed us to improve the accuracy and quality of our data regarding the median time to reperfusion, as well as the median anastomoses time, for open KT and RAKT cohorts. All data on anastomoses time and re-warming time have been carefully reviewed by two authors (R.C. and V.L.M.), in conjunction with the kidney transplantation anesthesiological team, through a systematic review of patients' electronic medical records. In particular, the anesthesiological team reports the exact timing of external iliac vein/artery clamping and de-clamping, as well as of kidney reperfusion. After this comprehensive reassessment, we published our data in a dedicated paper, that was under evaluation during the submission process for the current review. Therefore, we've modified the results on this item and the related reference:

   "*These favorable preliminary findings were confirmed by an updated analysis comparing RAKT and open KT from DDs at our Centre*[37]*. Overall, there were no significant differences between the RAKT and open KT cohorts in terms of baseline donor-, graft- and recipient-related characteristics, expect for a significantly higher proportion of pre-emptive recipients in the RAKT cohort (38.1% vs 5.1%, P = 0.0001), a significantly lower ASA score among patients undergoing RAKT (2 vs 3, P = <0.001). The re-warming did not significantly differ between RAKT and open KT (48 vs 47 min, P = 0.2).*

   There were no significant differences between RAKT and open KT in terms of median hospital stay (13 days) as well as the major postoperative complication rate. However, the RAKT group was associated with a significantly lower blood transfusion rate (14.3% vs 22.2%, P = 0.008). At the last follow-up, no differences were observed between the two groups in terms of mid-term graft function." (RAKT FROM DECEASED-DONORS: CHALLENGES AND PRELIMINARY RESULTS).

3. ***At the results section, this sentence is controversial. -"The proportion of patients experiencing Clavien-Dindo grade ≥ 3 surgical complications as well as the transfusion rate was lower in the RAKT group (15.0% vs 20.6% and 10.0% vs 15.7%, p=0.5 respectively). " Because a p-value of 0.5 does not signify a difference.***

   We thank the Reviewer for this comment. We've modified the sentence, in light of the updated data as mentioned above.

4. ***The following sentence is not understandable and unclear. -"At a median follow-up of 18 months (IQR 8-36), there were no significant differences in functional outcomes between RAKT and OKT." What is meant by the functional outcome? Graft survival? eGFR? Patient survival?***

   We thank the Reviewer for this kind comment. We've modified this sentence to avoid misunderstandings.

5. ***As you know, in the deceased donor setting the coordinating role between the donor hospital and recipient hospital is important. the donor coordinator perspective should be given. Even the requirement of a prior CT scan of the recipients is a burden for the coordinator's work.***

   We thank the Reviewer for this kind comment. We created a dedicated pathway that overcome the classical obstacles for the spread of this procedure, even in the DD setting.

   Our organization is based on the same harvesting procedure for both open and robotic procedures, avoiding any impacts on donors' centres.

   However, a carefully preoperative evaluation of patients is needed to perform all mandatory tests before the "emergency". In particular, CT is usually performed before the evaluation of eligibility for the robotic approach.

   To clarify this important point, we provide the following revisions to the manuscript:

   - *"Despite the development of a RAKT program from DD could be extremely challenging from both a technical and organizational standpoint, Campi et al[37] proposed the realization of a dedicated pathway, avoiding any impact on donors' management from both a clinical and organizational standpoint, even in the DD setting."* (DISCUSSION OF THE EVIDENCE AND FUTURE PERSPECTIVES)

- *"For these reasons, a carefully preoperative evaluation of patients is needed to tailor the surgical approach in light of patients' characteristics, especially when the procedure will carry out as an emergency."* (RAKT FROM DECEASED-DONORS: CHALLENGES AND PRELIMINARY RESULTS).

6. ***How about the cost of these robotic kidney transplant surgeries? I would like to receive more in-depth insights about this. Who pays the extra expenses regarding these additional costs?***

   We thank the Reviewer for this comment. As reported in our manuscript, no high-quality studies regarding the cost/effectiveness balance for RAKT have been carried out, yet.

   In our experience, Italy has a universal healthcare system, based on the Beveridge's model. Through taxes, the state provides medical procedures for all inhabitants, even robot-assisted kidney transplantation. In our experience, the overall impact of extra-costs is reduced thanks to the high number of robotic procedures (>2000 per year).

   We've underlined this item, as follows:

   "While an estimated increased cost of 15000 USD per RAKT has been reported[45] if compared to open approach, the higher availability of platforms will hopefully reduce the costs of robotic technology, mitigating the financial downside of RAKT in the future."

7. ***The discussion section lacks a novel conclusion.***

   We thank the Reviewer for this comment. We've reviewed the discussion in order to highlight some relevant points for the DD setting.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors did a very nice review. I have few questions for the authors.

1. ***Any information about the length of stay between both groups***

   We thank the Reviewer for this comment. The overall hospital stay could represent a relevant surrogate to evaluate an early recovery after surgical procedure. However, this

field could be influenced by several aspects such as hospital policies and patient-related factors. Among the evaluated studies, the median overall hospitalization ranged from 7 days to 14 days, providing similar outcomes to other European experiences, in particular we've modified the manuscript as follows:

- *"The median hospital stay ranged between 7 and 14 days [12,17] among the available studies, but it could be influenced by several items, such as hospital policies and patient-related factors."*(OUTCOMES OF RAKT FROM LD SETTING)

2. ***Could the authors specify what part of the world is getting ready for prime time?***

We thank the Reviewer for this kind comment. To date, the number of European centres that have developed RAKT programs is progressively increasing, and a dedicated training course has been created at ORSI Academy (Belgium). However, high costs remain the main obstacle to a larger spread of this procedure worldwide. Therefore, in light of the available evidence in terms of feasibility, reproducibility, and safety for RAKT and the possible cost cut for robotic surgery in the near future, we could take advantage of several unprecedented opportunities. Although there is still a lack of evidence regarding the real clinical impact of RAKT, we believe that the implementation of RAKT worldwide could provide high-quality data (*e.g.* randomized clinical trials) and more information regarding the decision-making process to identify those patients who could benefit the most by robotic surgery. In conclusion, given the expected reduced costs for robotic surgery, the potential spread of robotic platform across several centers worldwide and the advantages provided minimally-invasive approach, we believe that "*RAKT could get ready for the prime time*". (DISCUSSION OF THE EVIDENCE AND FUTURE PERSPECTIVES)

3. ***In the US, we have United Network for organ Sharing (UNOS) that manages the organ transplant system. The transplant programs are under a very strict monitoring of their compliance and performance. The programs could be penalized if their performance is below the National Standard. Which government institution or private will review the transplant program performance in the rest of the world?***

We warmly thank the Reviewer for this comment, which allowed us to investigate the role of international organization in the field of transplantation. While the USA created the United Network for organ Sharing (UNOS) as the organization that manages the organ

transplant system, currently, there is lack of international organizations, able to manage the transplant programs worldwide. To date, despite the development of a common legislative framework, the European Community hasn't provided a unique organization able to coordinate and evaluate the transplant centers across European countries. In fact, national competent authorities are responsible for implementing the requirements established by EU legislation. The European Commission holds regular meetings with these authorities to facilitate the exchange of best practice. Currently, three European organization have been created to coordinate the organ sharing process across different countries (Eurotransplant, Scandiatransplant and the south Alliance for transplant), but they can't evaluate the performance of each included centres. Therefore, we believe that the realization of a strong European organization with a clear mission of surveillance and coordination across national centers could represent a relevant step forward in this field, providing a common legislative framework, common standards and improving the overall results.

4. ***We have one of the largest kidney program in the US and our median for both vascular anastomosis is 30 minutes. Could they explain why median of 62 minutes for both vascular anastomosis in the open procedure?***

We thank the Reviewer for this comment, which allowed us to improve the accuracy and quality of our data regarding the median time to reperfusion, as well as the median anastomoses time, for open KT and RAKT cohorts. All data on anastomoses time and re-warming time have been carefully reviewed by two authors (R.C. and V.L.M.), in conjunction with the kidney transplantation anesthesiological team, through a systematic review of patients' electronic medical records. In particular, the anesthesiological team reports the exact timing of external iliac vein/artery clamping and de-clamping, as well as of kidney reperfusion. After this comprehensive reassessment, we published our data in a dedicated paper, that was under evaluation during the submission process for the current review. Therefore, we've modified the results on this item and the related reference:

"*These favorable preliminary findings were confirmed by an updated analysis comparing RAKT and open KT from DDs at our Centre*[37]*. Overall, there were no significant differences between the RAKT and open KT cohorts in terms of baseline donor-, graft- and recipient-related characteristics, expect for a significantly higher proportion of pre-emptive recipients in the RAKT cohort (38.1%*

vs 5.1%, P = 0.0001), a significantly lower ASA score among patients undergoing RAKT (2 vs 3, P = <0.001). The re-warming did not significantly differ between RAKT and open KT (48 vs 47 min, P = 0.2). There were no significant differences between RAKT and open KT in terms of median hospital stay (13 days) as well as the major postoperative complication rate. However, the RAKT group was associated with a significantly lower blood transfusion rate (14.3% vs 22.2%, P = 0.008). At the last follow-up, no differences were observed between the two groups in terms of mid-term graft function." (RAKT FROM DECEASED-DONORS: CHALLENGES AND PRELIMINARY RESULTS).

5. ***Best surgical approach to treat urological complications***

   We thank the Reviewer for this comment. We've discussed this topic in the DISCUSSION OF THE EVIDENCE AND FUTURE PERSPECTIVES:

   "On this regard, while Musquera et al[17] reported two patients treated through open ureteral reimplantation for stenosis, Campi et al[37] reported two cases of endoscopic management for ureteral complications in DD setting. Therefore, the best surgical approach to treat urological complications should be evaluated in light of patients' and related-problems characteristics (endoscopic, minimally-invasive surgery or open approach)."

6. ***Could the authors describe, in their review, recommendations to avoid vascular recommendations?***

   We thank the Reviewer for this comment. We've developed this interesting item in the SURGICAL TECHNIQUE FOR ROBOT-ASSISTED KIDNEY TRANSPLANTATION, as follows:

   "During the procedure, a careful management of vascular anastomosis is mandatory to reduce the risk of severe postoperative complications. In particular, avoiding intimal injury, thorugh a delicate manipulation of graft vessels represents a key step during RAKT. In addition, as suggested by Gallioli et al[19] a complete learning curve could be usefull to achieve reproducible intra- and postoperative outcomes."

7. ***Who should be performing the RAKT, a trained transplant surgeon or urologist or general surgeon doing robotic?***

We thank the Reviewer for this comment. We've added this topic to the DISCUSSION OF THE EVIDENCE AND FUTURE PERSPECTIVES:

"The available evidence regarding the learning curve assessment suggests potential advantages. As previously reported[11], surgeon's background has a limited impact to perform RAKT. What really matters is the previous surgeons' exposure to robotic surgery and open KT. However, considering the major exposure to minimally-invasive surgery and expertise in ureteral diseases, urologists may have significant advantages, if compared to other specialties (e.g. general surgeons, transplant surgeons…), as well as the abilities to manage the potential postoperative complications (e.g. ureteral stricture)."

8. ***Could the authors describe the indications for RAKT and contraindications?***

We thank the Reviewer for this comment. Currently, the absolute contraindications for RAKT are the presence of atherosclerosis calcification at the level of the iliac vessels and prior bilateral kidney transplantations, but some centers may have added other exclusion criteria in light of the specific setting and organizational pathways. On the other hand, the indications for minimally-invasive surgery in this field are still under debate. Therefore, increasing the available evidence in this field and improving the overall quality should represent a primary goal for the transplant community in order to provide a change of perspective: the surgical approach should be tailored in light of patients' and grafts' characteristics. In this view, some American centers have implemented RAKT programs for obese patients, who have a higher risk of wound infection. In addition to weight, other relevant factors should be evaluated to identify those patients, who could benefit the most from minimally-invasive surgery. We've added this information to the manuscript:

- *"The absolute contraindications were the presence of significant atherosclerosis plaques at the level of the iliac vessels, prior bilateral kidney transplantations, previous major abdominal surgery, second transplant and simultaneous dual or multiple organ transplant, and second transplantation." and*
- *"The exclusion criteria to perform RAKT have been modified during the last years, but the main issues are currently represented by severe calcification at the level of the iliac vessels and previous bilateral KT[17]."* (SURGICAL TECHNIQUE FOR ROBOT-ASSISTED KIDNEY TRANSPLANTATION)

9. ***Which is the recommended BMI to perform RAKT?***

   We thank the Reviewer for this comment. We've added this topic to the manuscript:

   "However, the optimal indications as well as the ideal body mass index (BMI) to perform RAKT is still under debate. Recently, some experiences regarding the outcomes for obese patients and morbidity obese ones (BMI ≥ 30 and 35 kg/m^2, respectively) have been reported, highlighting benefits in terms of postoperative wound infection if compared to open KT[40,43]. In addition, Spaggiari et al[44] have recently published the results about the simultaneous realization of RAKT and sleeve-gastrectomy, improving the patients' compliance and outcomes." (SURGICAL TECHNIQUE FOR ROBOT-ASSISTED KIDNEY TRANSPLANTATION)

10. ***Any complications after kidney biopsy in the RAKT group.***

    We thank the Reviewer for this comment. We've added this relevant issue to the SURGICAL TECHNIQUE FOR ROBOT-ASSISTED KIDENY TRANSPLANTATION:

    "…this step has been shown to offer a safe access for diagnostic and therapeutic percutaneous procedures during the postoperative period, as reported by Campi et al, who didn't report any type of postprocedural complications[26]".

11. ***The authors are concern about the fragility of KT recipients, maybe all the obese future transplant patients should have robotic bariatric surgery and then the transplant to improve the quality of life and decrease morbidity after the RAKT. Could the authors describe the complications seen in the morbid transplant recipient after RAKT?***

    We thank the Reviewer for this comment. We've discussed this topic in the DISCUSSION OF THE EVIDENCE AND FUTURE PERSPECTIVES:

    "However, the optimal indications as well as the ideal body mass index (BMI) to perform RAKT is still under debate. Recently, some experiences regarding the outcomes for obese patients and morbidity obese ones (BMI ≥ 30 and 35 kg/m^2, respectively) have been reported, highlighting benefits in terms of postoperative wound infection if compared to open KT[40,43]. In addition, Spaggiari et al[44] have recently published the results about the simultaneous realization of RAKT and sleeve-gastrectomy, improving the patients' compliance and outcomes[44]."

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: This minireview focuses on robot-assisted kidney transplantation, an alternative approach to open surgery.

1. ***The authors mentioned the benefits, better exposure to the surgical field, better instrument maneuverability, the possibility to integrate other technological nuances, and cadaver donation, which is of some significance to the clinical field. However, the writing of the minireview has certain limitations and the discussion section lacks a novel conclusion.***

   We thank the Science Editor for this comment. We've revised the discussion to provide a better overview of the main nuances in this field.

2. ***Besides, the form of the table in the minireview should adopt the form of a three-line table.***

   We thank the Science Editor for this suggestion. We've corrected the format, as requested.

(2) Company editor-in-chief: 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 Transplantation, 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.

1. ***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.***

   We thank the Editor in chief for his help. We've prepared and arranged the figures using PowerPoint, as requested.

2. ***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) 2022. 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. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

We thank the Editor in chief for his help. We've prepared and arranged the figures and tables, as requested.