



PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 40339

Title: Clinical features and determinants of VO₂peak in de novo heart transplant recipients

Reviewer’s code: 03742333

Reviewer’s country: United Kingdom

Science editor: Fang-Fang Ji

Date sent for review: 2018-07-02

Date reviewed: 2018-07-02

Review time: 16 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer’s expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I have read with great interest the study entitled “Clinical features and determinants of VO₂peak in de novo heart transplant recipients”. Initially, I would like to congratulate the authors for the efforts to develop this multicentre study. The paper is well written



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and add relevant new data in the field. The authors examine a cohort of 81 patients after de novo heart transplant and following a thoughtful analysis conclude that cardiac (O₂ pulse and HR reserve) and peripheral factors (muscular exercise capacity) predict the peak of oxygen uptake in an early stage. The study has merit however I truly believe that some important issues should be addressed. General comments: The number for a clinical trial is provided. According with this number the study is described as an interventional randomized clinical trial and has as interventions moderate and high intensity interval training. However, the abstract starts already saying that this is “cross-sectional analysis”. If I am not wrong the data from a clinical trial was used in this observational study? This is an important point that the authors need to clarify as there are huge differences between randomized clinical trials and observational studies. A cross-sectional study, as the study is classified in the abstract, applies one test at a set point in time and assess the prevalence of one factor. However, as it does not have an evolution in time, any causal relationship should be carefully assessed. If this is really the case, this is a limitation that should be acknowledged in the discussion. Accordingly, the CONSORT 2010 statement is said to be reported. However there is not a single answer in the form uploaded. Therefore, if the authors intend to report the results of a clinical trial many elements are missing, such as clear definition of intervention groups, clear end-points of the study and inclusion/exclusion criteria. Was the study randomized? Which technique of randomization was used? Title: This is a journal of transplantation in general, I would consider replace the abbreviation VO₂ peak by peak oxygen consumption as it is easily understandable for non-cardiac transplant professionals. Abstracts: According with the former comment, the aim could contain some background to contextualise readers about the importance of the subject and VO₂ peak and HTx. Method section has a wrong typo “performed mean 11” and also should explain how experimental groups were defined. Results mention a general population



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that was not defined as included in the study. I would wonder if this is a third group? Moreover, how psychosocial function was assessed? Is this relevant to be included in the abstract? Conclusion says “central and peripheral factors” however these factors were not described previously. Introduction: This section would benefit from more clarification of what is the importance of VO₂ peak and define which are the central and peripheral factors. Methods: All general comments apply in here. Was this an interventional clinical trial? How sample size was determined? What was the end-point used to power the study? Results: Really long table 1 making difficult the interpretation. Is it possible to split the table by different topics? The n in the table varies from 63 to 81, this means that more than 20% of the population is missing for some analysis. This is a factor that can significantly affect results, maybe one column with the n used in each analysis could make readers aware of limitations of some analysis. Discussion: It starts saying “as compared with a general population”. I cannot find a third group compared in the study. Therefore I assume you compared with figure reported by previous studies, this should be better explained to avoid confusion. Is there any limitation that readers should be aware? Please comment.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 40339

Title: Clinical features and determinants of VO₂peak in de novo heart transplant recipients

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Reviewer's country: United States

Science editor: Fang-Fang Ji

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

A well done study, but with limited scope. The concept of frailty is increasingly being recognized as a factor influencing long term renal transplant outcomes. while true that Vo₂ measurements helps frame expectations of functional capacity post heart



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transplants, the much more interesting question in my mind is -outcomes. Does a reduced VO2 max predict increasing risk of heart failure, death, rejection, sepsis and/or infection? these remain to hopefully be seen in future publications. The publication is of professional quality-and I will recommend publication. Though many interesting variables remain to be explored from the population you are following linking functional exercise testing with outcomes would be a high quality publication needed in heart transplant literature.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 40339

Title: Clinical features and determinants of VO₂peak in de novo heart transplant recipients

Reviewer's code: 03291363

Reviewer's country: Australia

Science editor: Fang-Fang Ji

Date sent for review: 2018-07-02

Date reviewed: 2018-07-06

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The major concern I have is the study design. There is no comparator or control group to compare the findings in de novo heart transplants. These controls could be the general population and/ or maintenance heart transplants. Second there is no longitudinal



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data to establish the validity of the time selected in the post op course of the recipients. Finally I think that the authors should state the hypothesis clearly at the outset in the paper. Hence given the above it is difficult to draw the conclusions of the study namely that there are three determinants of the cardiorespiratory exercise tolerance in de novo heart transplant recipients. But the paper is well written, the graphs and tables clearly presented and the discussion relevant although too long. A lot of work has gone into this study. The topic itself is important in the care of these heart recipients post op.

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PEER-REVIEW REPORT

Name of journal: World Journal of Transplantation

Manuscript NO: 40339

Title: Clinical features and determinants of VO₂peak in de novo heart transplant recipients

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Reviewer's country: Chile

Science editor: Fang-Fang Ji

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Review time: 5 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
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		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
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SPECIFIC COMMENTS TO AUTHORS

Comments on Clinical features and determinants of VO₂peak in de novo heart transplant recipients Introduction Nice introduction. It is concise and clear, but, dismisses that some interested readers could not understand what are the central and



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peripheral factors determining O₂ consumption. At first glance, it is not easy to imagine why is not the transplanted heart itself the most important factor, I suggest to add a brief explanation that, at the same time, could be useful to understand the manuscript aim that follows: "Determine clinical, hemodynamic end peripheral factors that contributes to explain the reduced exercise capacity". Are the clinical factors not related to hemodynamics? Material and Methods It is confusing that 72 from 155 patients were excluded because they did not meet the I/E criteria considering that they are very broad: "Clinically stable HTx recipients approximately 8-12 weeks after HTx; Age > 18 years; Both sexes; Receiving immunosuppressive therapy according to local protocols; Patient willing and able to give written informed consent for study participation, and motivated to participate in the study for nine months". I presume that all were adult HTx patients receiving immunosuppression. As the authors explain, measuring oxygen consumption (VO₂ peak) is part of the standard postoperative care of HTx patients in the participating hospitals, so it is improbable that the patients did not consent to undergo the cardiopulmonary exercise test (CPET). Could it be that some patients did not participate because they were too ill? If this explanation is true, maybe the real VO₂ peak measurements could be much worse than 19.4 ml/Kg/min. Which were the differences between recruited and not recruited patients? The tables state that "63-81" patients (first columns) conform the two study groups. Those number differ from the 72 patients recruited. In the Abstract section it appears 81 as the studied sample. Measurements: This section begins with: "The primary endpoint, VO₂peak". Is VO₂ peak and outcome or a measurement? Consider that this variable comes for a measurement and, for this same reason, it is an independent variable. The "secondary endpoints" are several other independent variables that could influence or modulate the "primary endpoint" or main independent variable. All these are confusing, especially considering that the redaction of this subsection seem to describe a next multivariate



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analysis. Were all measurement performed in the same opportunity with VO₂ peak? QoL questionnaires too? Statistical analysis: The authors used several statistical tools after dividing their samples in two halves (bellow or above the mean). Most of the time this kind of analysis compares first and last tertiles or quartiles. Are Cohen's kappa statistic as high to, in fact, differentiate exactly those patients having VO₂ peaks 19.3 vs 19.5 ml/Kg/min if they perform a CPET twice? From this subsection, it is clear that VO₂ peak could be considered a binary primary endpoint after concluding a proper logistic analysis. Authors state: "To identify the degree of association with VO₂peak, all relevant variables with P < 0.05", It seems that they test everything!! If this is true, p-values must be accordingly adjusted for multiple comparisons to be considered significant. Results The description is clear and concise. Low VO₂ peak patients are sicker than the high VO₂ peak ones. The most interesting finding in this section is those poor performance patients seem to have lower left ventricular ejection fraction, higher NT-pro-BNP and to use lower doses of immunosuppressive agents: Were differences in heart rejection rates between both groups? As pre transplantation demographic and clinical characteristics are comparable in both groups, most findings could be explained by post-operative events and immunological injuries after HTx are examples of those events. From Table 1 exploration: Do authors think that the two study groups are as comparable as their p-values suggest or could it be that the small study sample preclude to find real existing differences (type 2 error)? From Table 1: Is this figure correct? LVEDD (cm) 4.9 ± 0.5 4.9 ± 0.5 4.9 ± 0.4 0.996 0.39 [0.19, 0.59], <0.001 I did not find the description of Table 3. Nevertheless, the multivariate analysis resulted that the predictors of above or below the mean VO₂peak are two variables resulting from the same CPET (O₂ pulse and HR reserve) and from muscular exercise capacity. Do authors think that these findings could disincentive clinicians and physiotherapist to perform CPETs, even this test been safe? Graphs are nice and clear. Discussion This section is round! Well and clearly written. I



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suggest to include my above commentaries to this section and to think if some of the findings could be explained because most patients were heart transplanted too late. Abstract and Core tip sections are both OK. In summary. The manuscript is not yet fitted to be published, but, if some modifications are wisely added, it will.

INITIAL REVIEW OF THE MANUSCRIPT

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- No

BPG Search:

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