Thessaloniki 7/6/2022

Prof. Vassilios Papalois, MD, PhD, FEBS, FICS, FRCS

Editor in Chief,

Prof. Georgios Tsoulfas, MD, PhD, FACS

World Journal of Transplantation,

Dear Prof. Papalois and Tsoulfas,

Please find attached the revised version of our Invited Review entitled "Hypertension in kidney transplant recipients" for publication in the **Special Issue "Translational research and innovation in modern transplant practice: paradigms from Greece and around the world"**. We hope you will accept this resubmission, as all comments and suggestions from the Reviewers and the Editorial Board have been taken into consideration and we proceeded to detailed answers and revisions accordingly.

You will find our numbered responses addressing in detail each comment or suggestion of the reviewers in the following pages. All the additions and changes made have been clearly indicated in red.

We will be happy to provide any additional information that you might find necessary in order to consider our paper for publication. We look forward to hearing your final decision.

Best regards,

Pantelis A Sarafidis, MD, MSc, PhD, Associate Professor of Nephrology, Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Konstantinoupoleos 49, GR54642, Thessaloniki, Greece. Tel/Fax: +30 2313 312930. E-mail: psarafidis11@yahoo.gr

We would like to thank the expert Reviewers for their comments and for their effort in reviewing our manuscript. Each of their comments are addressed as follows.

Reviewer #1			
No	**Comment**	**Response**	**Page in the Revised Manuscript**
1.	24-h ABPM outperforms office BP measurements for kidney transplant recipients. Dihydropyridine CCBs are recommended to treat hypertension of kidney transplant recipients. It has guiding significance to clinic.	We thank Reviewer #1 for his comments on our Manuscript.	
Reviewer #2			
In this review article about Hypertension in kidney transplant recipients, Alexandrou et al have summarized the etiology and			

management of HTN in kidney transplant recipients. It is well written and clear. However, it lacks novelty. There are 100's of papers in this field, so I am not sure what will be added in the field with this review article.			
1.	--Would focus more on the secondary causes of HTN, and work up pertinent to the kidney tx	We appreciate this comment from the Reviewer #2. With regards to the manuscript's originality, we would like to inform the reviewer that this was an invited review for a special issue. We are happy however to enrich parts of the manuscript relevant to secondary causes specific to kidney transplantation according to his suggestion. The text now reads: 1) (Revised Manuscript, Page 12) "*Other factors related to donors, predisposing to delayed graft function and increased nephrotoxicity, that could be possibly associated with development of hypertension in KTRs include the presence of genetic variants that affect the expression of cytochrome P450 3A5 (CYP3A5), apolipoprotein L1 (APOL1), P-glycoprotein (ABCB1) and multidrug resistance protein 2 (ABCC2) [81–83].*"; 2) (Revised Manuscript, Page 12) "*Moreover, longstanding hypertension may be present in many recipients before transplantation, as progression of CKD is associated with atheromatosis of middle-sized conduit arteries and most importantly with reduced compliance and arterial stiffness of aorta and the large arteries[85]. This vascular remodeling may not be fully reversible after kidney transplantation*"; 3) (Revised Manuscript, Page 14) "*Acute rejection may trigger new-onset hypertension, probably via activation of the*	Pages 12, 14

		renin-angiotensin system according to patient's volume status; in this case treatment of rejection is accompanied by improvement in BP levels, whereas hypertension non-associated to acute rejection would be further deteriorated with modifications in doses of immunosuppression[93]; 4) (Revised Manuscript, Page 14) "*Patients with positive AT1R antibodies represent a subset of those with antibody-mediated rejection in whom kidney dysfunction is associated with malignant hypertension and acute vascular lesions on biopsy. A clinico-pathological entity including seizures on top of malignant hypertension and vasculopathy has been also described, bearing resemblance to pre-eclamptic syndromes where AT1R antibodies have been previously reported [95].*	
2.	--Role of immunos and CNI minimization	We thank the Reviewer #2 for this suggestion. The following parts have been now added with regards to the role of immunosuppression and minimization of CNIs: 1) (Revised Manuscript, Page 10) *"The burden of long-term corticosteroid exposure on corticosteroid-related adverse events and healthcare economic costs has been previously explored in the general population, as well as in KTRs, with prevalence of corticosteroid-induced hypertension estimated to exceed 30% of the total population[59] and hospitalization costs to be 2.2-fold higher in the steroid-maintenance group than in the steroid-free group one-year post living-donor kidney transplantation [60]";* 2) (Revised Manuscript, Page 11) *"After complete withdrawal of CNIs was abandoned*	Pages 10, 11, 12

		due to an increased risk of biopsy-proven acute rejection episodes[71], reduction of their dose was explored in an attempt to minimize their toxic effects. In an open-label RCT, 1645 KTRs were randomly allocated to receive standard-dose cyclosporine (target trough level 150-300 ng/mL for the first 3 months; 100-200 ng/mL thereafter), low-dose cyclosporine (target trough level 50-100 ng/mL throughout the study), low-dose tacrolimus (target trough level 3-7 ng/mL throughout the study), or low-dose sirolimus (target trough level 4-8 ng/mL throughout the study) for 12 months[72]. Patients in all treatment groups received mycophenolate mofetil and corticosteroids; those randomized to low dose regimens followed a 2-month induction treatment with daclizumab. At study-end, patients in the low-dose tacrolimus group had the highest eGFR (65.4 ml/min) and highest rates of allograft survival (94.2%), followed by low-dose cyclosporine (93.1%), standard-dose cyclosporine (89.3%) and low-dose sirolimus (89.3%) (p=0.02), therefore providing further evidence in favor of low-dose tacrolimus regimens"; and 3) (Revised Manuscript, Page 12) *"Belatacept is another biologic immunosuppressive agent that acts by inhibiting T-cell co-stimulation, approved by the United States Food and Drug Administration (FDA) since 2011 on the basis of evidence of non-inferiority in preventing acute rejection in KTRs provided from three RCTs comparing belatacept to cyclosporine [69,73,74]. According to a meta-analysis (5 studies, 1535 participants) use of belatacept has been associated with lower BP levels and*	

		reduced incidence of chronic kidney scarring compared to CNIs [75].”	
Revision reviewer			
1.	Thanks for answering my questions. I have no new comments.	We thank for your comments on our Manuscript.	
		Science Editor	
1.	The manuscript is well written and the topic has clinical significance. Language Quality: Grade B (Minor language polishing) Scientific Quality: Grade C (Good)	We thank the Science Editor for this comment. We have now proceeded to a major revision addressing all Reviewers’ comments. A meticulous language polishing of the Revised Manuscript, ensuring that all grammatical, syntactical and formatting and errors were resolved, has been undertaken by a native English-speaking expert that is included among authors.	
Company Editor-in-chief			
1.	I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which	We thank the Company Editor-in-chief for his comment. As stated above, we have proceeded to a major revision of the Manuscript. Standard three-line table has been provided according to the Journal’s Guidelines. The latest cutting-edge research articles have been included in the Revised version of the Manuscript.	

	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. 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/.		