"Answering litter"

Reviewer **03291363**	Answers
Authors have made an extensive review of published work in PTLD. My comments are: • Study *design* is not elucidated. • PI explain and in particular what *statistical analyses* were done to determine the *adequacy* of these studies. Do they have type 1 or type 2 errors for example?	- ***Design:*** A thorough revision of the literature as regard PTLD epidemiology, risk factors, salient features, prophylaxis and the current therapeutic options has been admitted. Transplant recipient's chance of re-transplantation has been also deeply discussed. - Our study is a systematic review, revising the published work in PTLD that is mostly cohort studies, retrospective studies of the various PTLD registries, prospective studies and case reports. Critical appraisal (CASP) of the published articles is beyond the scope of this review. Furthermore, in view of rarity of PTLD patients, RCT (randomized controlled trials) cannot be admitted, so, no room for type 1 or type 2 errors evaluations. However, the most recent trial of PTLD management (PTLD- 2) is already discussed and summarized in p 25. It is a prospective multicenter interventional (clinical) trial enrolling patients, with risk stratification based on the response to rituximab, International Prognostic Index (IPI) score, and type of organ transplanted. It is noteworthy to clarify the evolution of the "Rituximab-based Treatment Protocols for PTLD after Solid-Organ Transplantation" have been progressed in four phases: I. Prospective phase 2 trials evaluating rituximab monotherapy. II. Sequential treatment in the PTLD-1 trial: Patients were enrolled in this portion of the trial from 2002 through 2008. III. PTLD-1 trial for risk-stratified sequential treatment: Patients were enrolled in this portion of the trial from 2006 through 2014 (*see please figure* 7). IV. On the basis of the PTLD-1 findings, the aforementioned prospective interventional trial (PTLD-2) is currently ongoing (Clinical Trials.gov number, NCT02042391).
• Although authors hv recommendations for management some are "hard or *established*" & some "*soft or experimental*". I think it would help the reader if those *established* principles were listed with the *evidence* and likewise for *experimental* group with *evidence*. Greater emphasis should be placed on *critical evidence base* to evaluate PTLD management that includes drugs used (e.g. *rituximab*), *viral load*; use of *CSF recovery* and other factors	Management: ❖ Currently, there is no therapies approved by FDA for PTLD. Commonly used agents for PTLDs include: rituximab (Rtx) (Rituxan®). If Rtx therapy was not satisfactory, other options may include: chemotherapy, radiotherapy and T-cell immunotherapy. ❖ Future (experimental) agents have been listed in "future therapies" page 24 (section: IV. Future strategies).
• Carcinogenic EBV is critical to PTLD and should be discussed.	**Added: Oncogenic EBV**: ***Mechanisms of oncogenesis***: EBV may alter cell growth via several mechanisms: (1) With lack of immune recognition, EBV may induce highly regulated growth transformation with expression of all of its growth inducing proteins. (2) Induction of the potent oncogenes e.g. LMP1 and LMP2 via environmental factors. (3) EBV induced proliferating cells as well as EBV variant/HLA types combination may permit these proteins to by-pass immune control and go

	unrecognized. (4) Growth alterations with the right levels of expression of cell targets and viral and cellular mRNA. ***Diagnosis:*** Serology: via viral capsid antigens (VCA-IgG) antibody detection is the best solitary serological test to indicate previous EBV exposure. Molecular testing: essential diagnostic technique in immunocompromised TR, where serology can be confusing and unclear owing to the erratic humoral response. Consequently, molecular plus serological methods combination may allow early detection of EBV infection. ***Prophylaxis***: Healthy donors may carry the high-risk variants of LMP-1 that predispose to malignant evolution. Understanding EBV molecular epidemiology in various populations and recognition of virulent strains can help in institution of a robust preventive strategies of PTLD. *Smatti MK, Al-Sadeq DW, Ali NH, Pintus G, Abou-Saleh H and Nasrallah GK. Epstein–Barr Virus Epidemiology, Serology, and Genetic Variability of LMP-1 Oncogene Among Healthy Population: An Update Front. Oncol., 13 June 2018 https://doi.org/10.3389/fonc.2018.00211* ***Therapeutic targets***: in view of the better understanding of these underlying mechanisms, each one may admit a potential therapeutic target, e.g. (1) Cytotoxic T-cell immunotherapeutic agents targeting EBV proteins. (2) Critical pathways (activated by EBV) blockers e.g. NFkB, PI3kinase, EGFR, can block critical activation locations of EBV oncogenes. *Raab-Traub N. Novel Mechanisms of Oncogenesis by the Epstein Barr Virus Curr Opin Virol. 2012 Aug; 2(4): 453–458. Published online 2012 Aug 1. PMID: 22858118 Doi: 10.1016/j.coviro.2012.07.001*
• Authors claim in the introduction: there is "*growing incidence* of PTLD": please provide *evidence.*	- Not seen in the "introduction", however, in "*epidemiology*", it is amended to increased awareness of PTLD prevalence.
• It should made clear that *immunosuppression* is risk factor for almost all cancers in tx and those risks can be increased by immunosuppression used to treat *primary renal disease* before RTx.	Added: Of note, the presence of previous exposure to immunosuppressive load during treatment of the primary renal disease in the native kidney is unnoticed risk factor for PTLD development.
• Remove *emotional words* such as "*devastating* disorder".	Done: Transplant clinicians should be vigilant to this *serious* disorder.
• *Writing style*: repetition, grammar, meaning of some sentences.	- Revised.
Reviewer II **03317108**	**Answer**
• It is a comprehensive and well-written review on Post-transplantation lymphoproliferative disorders (PTLD) covering any aspects of the disease. The discussion on the treatment of PTLD is clear. I would recommend the publication of this manuscript in the journal.	❖ Thank you Sir.

Reviewer III **00209021**	Answers
• Authors undertook a review concerning PTLD. They should be congratulated for this high quality review. The manuscript is well-written with adequate reference to the current medical literature in the field. The content of the text is satisfactory enough and the figures are informative. The review can be published for educational purposes especially for clinicians in the field after minor revision.	❖ Thank you Sir, we appreciate your precious words.
• Authors must replace "EPV" with "EBV" in Figure 4.	❖ Done, Sir (Figure 4).