Reviewer's Comments	Author's Reply
Reviewer #1 I applaud the authors effort to write this manuscript. The authors have described the various malignancies in significance to the transplant population which is relevant to a clinician.	Authors express their sincere gratitude for reviewing the manuscript and providing with suggestions for further improvement.
The only comment I have is this is a repetition of the publishes literature and most of these things can be found in various guidelines in literature.	The authors attempt to write a manuscript regarding post-transplant malignancy, with a particular focus on virus-associated aetiologies, and reviewed various literature sources to support their conclusions. To the best of our knowledge, the literature lacks a comprehensive, up-to-date review of the various post-transplant virus-associated aetiologies and their likely pathogenetic differences compared to the general population, the current status of adoptive immunotherapy in the treatment arsenal, and at the same time covering prevailing aspects pertaining to the topic.
Reviewer #2 This is a good article that gives an overview of risks and causes of significant morbidity and mortality of post-transplant malignancy.	Thank you for your insightful comments, analysis and feedback for refining the manuscript.
1. The author should clearly state which organ transplant is susceptible to what kind of virus.	Susceptibility of viral infections is proportional to the degree of net immunosuppression and varies greatly due to inherent limitations in the available data. The availability of population registry data for specific viral infections related with the type of organ transplant is insufficient, differs with immunosuppression regimen and geographical distribution and is, in general, weak worldwide. Upon conducting a thorough literature search, the authors could find EBV and HHV8 susceptibility with the type of organ transplanted. Incidences of PTLD risk is highest for intestine and multi-organ transplants (12 to 17 percent), followed by

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<td>lung (6 to 10 percent), heart (3 to 5 percent), liver (2 to 3 percent), and kidney (1.5 to 2.5 percent), being the least (1).
KS incidence varies with organ transplant and reported as per 100,000 person-years. It was reported as 95.79 (95% CI 42.81–214.31) in kidney, 44.25 (95% CI 4.78–409.20) in liver, 49.25 (95% CI 2.48–977.84) in heart and 10.97 (95% CI 4.12–29.23) in lung, respectively(2).</td>
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<td>2. The author said that each drug had risks of causing certain types of cancers. Could the author state more clearly which duration of taking the drugs would increase the risk of cancer?</td>
<td>Literature lacks evidence on how many years of use of immunosuppression post-transplant increases the risk of cancer. Despite uncertainties, literature consistently indicates that the overall duration and intensity of immunosuppression, rather than individual drug in immunosuppression regimen, lead to an increased risk of cancer.</td>
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<td>3. The author should be more specific about the carcinogenic mechanism of the virus.</td>
<td>Specific carcinogenic mechanisms of viral infections have been added in the manuscript as mentioned in Table 1 (3)
<table>
<tr><th>Virus</th><th>Carcinogenic mechanism(s)</th></tr>
<tr><td>EBV</td><td>EBV-infected cells generates more interleukin-6(IL-6), which promotes the proliferation of B-cells, and interleukin-10(IL-10), an immunosuppressive cytokine that promotes tumour development.</td></tr>
<tr><td>HPV</td><td>E6 and E7 proteins expressed by HPV suppress p53-mediated apoptosis and increase malignant growth in infected cells..</td></tr>
<tr><td>HHV8</td><td>Viral proteins encoded by HHV8 inhibit the activation of pro-caspase-8, promotes Ras-Phosphoinositide 3-kinase-Akt (Ras-PI3K-Akt) survival pathway and enhances antiapoptotic Bcl-2 expression (B-cell lymphoma 2), thereby inhibiting apoptosis and promoting uncontrolled proliferation of infected and endothelial cells</td></tr>
<tr><td>HBV</td><td>HBx proteins produced by virus activate the Ras-PI3K-Akt survival pathway and change epidermal growth factor receptor (EGFR) signalling.
In addition, it modifies the transcriptional activity of c-Myc, c-Fos, and c-Jun and</td></tr>
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<td>4. If the duration of using immunosuppressive drugs is short, such as in a liver transplant (2 years), is there any risk of carcinogenesis?</td>
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<tr><td></td><td>promotes the expression of angiogenic factors, including vascular endothelial growth factor (VEGF) and angiopoietin-1. Consequently, this stimulates proliferation and angiogenesis.</td></tr>
<tr><td>HCV</td><td>Virus-produced non-structural (NS) proteins (NS3 and NS5A) promote the Ras-PI3K-Akt survival pathway. NS5A also modulates the signalling mediated by epidermal growth factor receptor (EGFR). Consequently, this stimulates proliferation and angiogenesis.</td></tr>
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Current data suggests that the liver is an immunologically favourable organ and immunosuppression withdrawal is reported in well selected patients who had underwent liver transplantation (i.e. up to 40% of adults and 60% of paediatric liver recipients)(4). As data have not been specified in most clinical studies, usefulness of immunosuppression withdrawal in carefully selected liver transplant recipients has not demonstrated a significant clinical benefit on de novo malignancies post-transplant(4). Hence, there is risk of carcinogenesis.
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<td>Reviewer #3:
I compliment the authors for the effort put into writing this article and including a considerable number of references.

But I feel there are too many imperfections in writing style as well there are also some incorrections.

Among others, I could quote attributing most post-transplant cancers to a viral cause.</td>
<td>The authors are extremely grateful for your compliment and advises which are crucial for improving the manuscript's quality.

We(authors) have revised this manuscript for errors and corrections.

The types of post-transplant malignancies differ from those found in the general population.
In the literature, viral aetiology is well known and accepted as a probable association or causation (either promoting or inducing) of a wide variety of post-transplant malignancies.</td>
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I also did not understand the rationale behind using this term, "adoptive immunotherapy". Was it made up by the authors? That should be made clear. Regarding HCV-related post-transplant cancers, it must relate to post-transplant cirrhosis, which should also be mentioned.	Rosenberg and colleagues first described the efficacy of adoptive immunotherapy in murine tumours in 1987, and later demonstrating objective tumour response in metastatic melanoma patients(5,6). We have included a brief mention of the history of adoptive immunotherapy in the manuscript. HCV infection is also related to post-transplant cirrhosis and thereby increasing the risk of post-transplant HCC(7). This has been added in the manuscript
Company editor-in-chief comments: I recommend the manuscript to be published in the World Journal of Meta-Analysis. 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	Authors are delighted and extremely grateful for acceptance of this manuscript Thank you for recommending the RCA tool, which enabled us to improve the quality of the manuscript using this cutting edge artificial intelligence technology.

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.	

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6. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer. 2008;8(4):299-308.
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