

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Transplantation*

**Manuscript NO:** 74763

**Title:** Gastrointestinal manifestations, risk factors, and management in patients with post-transplant lymphoproliferative disorder: A systematic review

**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05077783

**Position:** Editorial Board

**Academic degree:** MD, MSc

**Professional title:** Assistant Professor, Surgeon

**Reviewer's Country/Territory:** Brazil

**Author's Country/Territory:** United States

**Manuscript submission date:** 2022-01-07

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-01-25 13:33

**Reviewer performed review:** 2022-02-01 14:18

**Review time:** 7 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No
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## **SPECIFIC COMMENTS TO AUTHORS**

The authors present a review on gastrointestinal manifestations of PTLT. The review is comprehensive, concise and well-written, and increases clinician awareness of an increasingly common condition. Some topics could be further elaborated on the manuscript. In page 4 line 29, the authors report acute cellular rejection as a well-recognized risk factor for the development of PTLT. It would be interesting to further discuss the underlying physiopathology - whether this increase is associated with the treatment of acute rejection (usually an increase in immunosuppression) or with the immune process of rejection itself. In page 4 line 36 oncogenic viral infection is cited as a risk factor for PTLT - the most common types of virus (EBV, etc.) could be cited here. The choice of treatment for PTLT is vague in the manuscript, the authors could further detail in what situations the reduction of immunosuppressive drugs is sufficient, and when should chemotherapy and immunotherapy be used. While on page 6 line 37 it is stated that the difference between outcomes in surgery and immunotherapy are not well elucidated, but in page 5 line 21 it is stated that surgical resection is rarely considered in patients with PTLT, this point should be clarified.

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**Peer-review model:** Single blind

**Reviewer's code:** 05121314

**Position:** Associate Editor

**Academic degree:** FEBS, MD, PhD

**Professional title:** Assistant Professor, Surgeon

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** United States

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**Reviewer performed review:** 2022-02-07 14:34

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <b>Y</b> ] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [ <b>Y</b> ] No
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### **SPECIFIC COMMENTS TO AUTHORS**

The authors did not perform a systematic review, or at least this was not performed according to the PRISMA guidelines. They should include a PRISMA diagram, specifying what databases were searched and what was the search criteria. Furthermore for the study included in the review a more detailed analysis, specifying in a table all the relevant information should be presented. In the present way, it does not seem to be very detailed and comprehensive.

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**Peer-review model:** Single blind

**Reviewer's code:** 04738361

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Director, Research Scientist

**Reviewer's Country/Territory:** France

**Author's Country/Territory:** United States

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No
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#### **SPECIFIC COMMENTS TO AUTHORS**

Manuscript ID 74763 reviews the PTLT complication after solid or hematopoietic transplantation. The authors have reviewed the publications of the last 20 years and narrowed it down to 9 articles that were included in this study. Although this is an interesting work, several points should be considered. \* Please add page and line numbers. \* This manuscript lacks descriptive tables and figures. \* Please make a figure regarding organ involvement of PTLT. \* Please make a figure regarding the workflow of the treatment. \* Please make a table regarding the possible treatments including the readout of immunotherapies. \* The keywords that were searched are very limited.

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**Peer-review model:** Single blind

**Reviewer's code:** 05820375

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Consultant Physician-Scientist, Research Associate

**Reviewer's Country/Territory:** United Kingdom

**Author's Country/Territory:** United States

**Manuscript submission date:** 2022-01-07

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-02-04 12:26

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**Review time:** 11 Days and 8 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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## SPECIFIC COMMENTS TO AUTHORS

The authors have provided a nice overview of the most common presentations of GI PTLT after SOT or HSCT. However, I miss some depth mainly in the discussion and the search strategy is too unclear to be classified as a systemic review, especially for a journal with this impact factor. Please clearly indicate what type of articles were included, a flowchart (for example according to the PRISMA guidelines) with the total number of articles, how many after removal of duplicates, how many were included for full review assessment, how many of these were excluded and why. Please also provide a table with the data extraction from the included articles. If the authors are not able to provide this information, it would be better to call it a literature review instead of a systematic review. Results: - Paragraph 4: please indicate the percentage (56 (11.9%) patients). It would also be interesting to give more info regarding the other locations. - I would suggest moving paragraph 9 after paragraph 5 to have a better transition. - Regarding the therapies, first of all I'd mention to check the EBV status, as this is the first thing you do after diagnosis and may affect treatment. - Please clarify supportive therapy: I often do not give IV fluids, antibiotics or blood transfusion. I guess you mean IV fluids in case of dehydration due to diarrhoea, or tumour lysis, blood transfusion in case of anaemia (due to bone marrow involvement or bleeding). - Paragraph 14: ATG and alemtuzumab are IS therapies given for SOT, and increase the risk for PTLT, not part of PTLT therapy? Please check. Interferon alpha was used as a therapy for PTLT indeed, although it is now rarely used because of increased risk of acute rejection. I would list rituximab separately as a monoclonal antibody against CD20 and not as chemotherapy. - Paragraph 20: what was the control group? Discussion: I miss some

depth in the discussion, now it is more a summary of the results. To be accepted in this high-quality journal it will absolutely need some improvements. - At the beginning of the discussion I miss a discussion about the impact of the EBV status as a risk factor (especially EBV negative + high dose of IS during first year post-Tx gives increased risk). - I don't know if acute rejection itself was a risk factor for PTLT or rather the associated increase in IS. - The authors should give more information on PTLT and the different subtypes (PTLT is not just one disease entity). I would elucidate early vs late-onset PTLT (latter associated with worse outcome), monomorphic vs polymorphic, early and polymorphic almost always EBV-associated and with higher response chance of reduction in IS +/- rituximab. While in more advanced disease stages or histology types, you often don't do sequential therapy but start with RIS + ritux + chemo. I would give some information on reduction of IS (which is often a reduction of calcineurin inhibitor trough levels and stop of MMF/AZA). I would avoid the term immunotherapy, I'm not sure what the authors mean exactly. I would use rituximab. In the table with data extraction, it would be nice to give some information on the PTLT types in the included studies (e.g., median time to onset, localizations, % monomorphic/polymorphic). - The authors sometimes mentioned radiotherapy. This is not often used for GI PLTD, rather for CNS disease. Can you clarify for which disease localization radiotherapy was used in the studies? Conclusion: - Only 9 articles were included, so I would not call it an extensive literature review. - Treatment depends on several factors... I miss reduction of IS here (which is the mainstay), I'd again clarify what you mean by immunotherapy (I guess rituximab, and would just use this word). I'd say RIS 'can be' associated with acute graft rejection (often PTLT is considered a consequence of over-immunosuppression and RIS is not always associated with acute rejection) Please introduce the abbreviations in the main text the first time you use them (intro line 1: gastrointestinal (GI), line 2 post-transplant lymphoproliferative disorder (PTLT)) and

please use it consistently afterwards (line 7, 13) Typo's: abbreviations: HSCT instead of SCST, consistency in writing (nonspecific in abstract, non-specific in main text), results paragraph 20 colorectal lowercase.

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**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05526454

**Position:** Editorial Board

**Academic degree:** MBBS, MCh, MS

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** India

**Author's Country/Territory:** United States

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**Reviewer performed review:** 2022-02-16 18:19

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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<b>Peer-reviewer statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No
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#### **SPECIFIC COMMENTS TO AUTHORS**

I congratulate the authors for putting their efforts to compile this manuscript. My comments:

1. If authors could elaborate on occurrence of PTLD separately with respect to different solid organs.
2. The details about the immunosuppression drug regimen used for induction, maintenance in each category of transplant patient population.
3. If authors could add on some photographs of pathological slides, endoscopic appearance of the lesions of PTLD.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Reviewer's code:** 04738361

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Director, Research Scientist

**Reviewer's Country/Territory:** France

**Author's Country/Territory:** United States

**Manuscript submission date:** 2022-01-07

**Reviewer chosen by:** Jing-Jie Wang

**Reviewer accepted review:** 2022-03-29 13:32

**Reviewer performed review:** 2022-03-29 13:38

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [ ] Yes [Y] No

#### **SPECIFIC COMMENTS TO AUTHORS**

The authors have addressed my concerns and questions. I have no further comments.

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**Professional title:** Consultant Physician-Scientist, Research Associate

**Reviewer's Country/Territory:** United Kingdom

**Author's Country/Territory:** United States

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**Reviewer chosen by:** Jing-Jie Wang

**Reviewer accepted review:** 2022-03-28 17:16

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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Conflicts-of-Interest: [ ] Yes [Y] No

#### **SPECIFIC COMMENTS TO AUTHORS**

The article has been updated very nicely and now addresses exactly the things that were missing in the first version. The addition of the tables and figures is also an added value. This revision has certainly upgraded the manuscript to one of a good quality level.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Professional title:** Assistant Professor, Surgeon

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** United States

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**Review time:** 2 Days and 5 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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Conflicts-of-Interest: [ ] Yes [Y] No

#### **SPECIFIC COMMENTS TO AUTHORS**

The authors revised according to my suggestions and followed a systematic reviews methodology more accurately.