Name of journal: World Journal of Transplantation

Manuscript NO: 65395

Dear Editor,

Dear reviewers,

Thank you for your time to revise our Manuscript ID: 65395, Factors affecting complications development and mortality after single lung transplant.

Authors: Metodija Sekulovski, Bilyana Simonska, Milena Peruhova, Boris Krastev, Monika Peshevska-Sekulovska, Lubomir Spassov, Tsvetelina Velikova.

We have incorporated most of the suggestions made by the reviewers. Those changes are highlighted within the manuscript in red color. Please see below, in blue, for a point-by-point response to the reviewers' comments.

Reviewer #1 No. 05820375

Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

The manuscript by Sekulovski and colleagues is well-written and a pleasure to read, and provides a nice overview of LTx-related problems. However, since the title is "after SLTx" I do miss emphasis on the differences between SLTx and SSLTx. After all, a lot of these complications are not specific for SLTx and happen after LTx in general (cardiovascular, renal, AR/CLAD…). It would be nice to mention this, and highlight some of the differences between SLTx and SSLTx (highlight the part of native lung complications for example). (or rephrase the title to after lung transplantation in general)

- ✓ Thank you for your constructive comments and the good overall evaluation of our paper. We made the changes according to your specific suggestions.

Abstract "Its low morbidity and mortality rates" sounds a bit weird, especially as you highlight the risks and complications afterwards. I would nuance it that the immediate morbidity and mortality after transplantation is lower compared to SSLTx. (but the long-term overall survival is in general better for SSLTx)

- ✓ We appreciate your insightful comment. We acknowledge for not being completely correct. We corrected the abstract according to your comment.

Introduction - Likewise, I would nuance the lower morbidity and mortality rates compared to SSLTx.

- ✓ We appreciate your comment. We added additional information about this issue.

- ➢ Typo line 9: because "of" Post SLTx complications related to graft function
- ✓ We corrected our mistake.

- Line 9: I would rephrase to "early ventilator weaning during the first 12h is recommended" PGD

- ✓ We are grateful for the important note. We rephrased the line as you suggested.

- Line 7: I would rephrase it to immunological and inflammatory processes and "possibly" infectious agents

- ✓ Thank you for your comment. We have changed the sentence as you recommend.

Line 16: "have longer-term survival", would rephrase it to "have a better (long-term) survival"

- ✓ We appreciate your valuable note. We corrected the text according to your suggestions.

Regarding the risk factors for PGD, I would mention that these are possible risk factors, some of those listed are less likely to be risk factors (e.g., gender and race were not confirmed in large multicenter cohort studies) than others. I miss aspiration as possible risk factor.

- ✓ We think this is an excellent remark. We have added "aspiration" as a possible risk factor for PGD development in table 2.

You indeed mention the mechanisms related to a higher PGD incidence in SLT, I would highlight that this is a specific difference compared to SSLTx.

- ✓ Thank you for your valuable comment. We have pointed out that those mechanisms are mainly in SLT. You can follow up on our changes in the text.

In case of size mismatch: I would mention the type of size mismatch (i.e., lobar or undersized LTx)

- ✓ Thank you for your comment. We have added the information about size-mismatch as you recommend.

The transition "an inappropriate treatment strategy may affect long-term survival, leading to the development of CLAD" sounds a bit to straightforward, I would mention that this is because PGD is a risk factor for CLAD ("may affect long-term survival, since PGD is a risk factor for the development of CLAD").

- ✓ Thank you for your valuable comments. We corrected the terms as you recommended.

AR/CLAD - "ACR is a common complication after SLT". In my opinion, this sounds like it is a common complication after SLTx but not after SSLTx, which is not the case of course. The numbers you provide are also from all LTx patients.

- ✓ We appreciate your insightful comment. We acknowledge for not being absolutely correct. We corrected the data according to your comment.

Line 9: I would remove the "however".

- ✓ Thank for your comment. We have removed the word "however".

Line 14: I would rephrase to "Clinical antibody-mediated rejection is defined as the presence of…" (or mention something about the subclinical and clinical forms)

- ✓ We appreciate your constructive comment. We rephrased the sentence according to your recommendations.

- Line 18: "AMR should be better diagnosed". Absolutely agree! Maybe the authors can give some comments/reasons why? Limitation of C4d staining, inter-observer variability, relevance of non-DSA HLA…

  - ✓ The referee is right to point out these factors. We added them after the comment for better diagnosis.

- The information about ALAD is a bit too short in my opinion, and also not fully correct as you say is it frequently treatable with steroids – but this depends on the cause of course. I would give some examples of causes: allograft-related (e.g, AR, infection, anastomotic problems…) or non-allograft related (e.g. pleural).

- ✓ Thank you for your constructive comment. We added in the review relevant information about ALAD and conditions related to its development.

- Also "the diagnosis of CLAD can be assumed after 3 weeks" depends on the exclusion of underlying causes. After all, if ALAD was caused by an anastomotic stricture it is likely this will persist after 3 weeks (especially if no intervention) but this is not CLAD. "Conditions such as restriction and/or obstruction of airflow. are associated with CLAD development". It is for me not clear what the authors want to say (I assume that they want to mention that there are restrictive and obstructive forms of CLAD, but now I can interpret it that restriction due to obesity leads to CLAD). I would remove (or rephrase) this sentence.

  - ✓ We accept the suggestion and revise the paragraph accordingly.

- I would use the latest CLAD definition (Verleden 2019) which does not include specific causes leading to chronic loss of allograft function – with the subdivision into BOS and RAS phenotype (and ARAD not anymore)

- ✓ We have added the proper information from the paper written by Verleden et al.

- Saying that RAS is triggered by microorganisms is a bit too straightforward in my opinion. As there are other risk factors such as AR, especially AMR, and (chronic) inflammatory processes probably play an important role.

- We agree with the referee that written in such a way, it may be misleading. Therefore, we split the sentence and add the information.

- Likewise, the authors state that 50% of SLT recipients develop CLAD but this counts for SSLTx as well. Would clarify this.

- ✓ We appreciate insightful comments. We clarified the difference between ALAD and CLAD and different types of CLAD (obstructive, restrictive, or mixed pattern). We also corrected the definition of CLAD according to the study of Verleden et al. as you suggested.

- Figure 1: you give different causes of chronic loss of allograft function but this is not the same as chronic rejection/CLAD, would rephrase the title to chronic complications or something like that.
  - ✓ We agree with the referee and changed the figure text.

Technical complications - Line 9: would remove however;

- ✓ We appreciate your note. We have removed it from the text.

Typo: complex instead of complexed

- ✓ We corrected our mistake.

Associated factors: I don't fully understand the PGD example the authors are giving, I miss the most important factor "lack of perfusion" due to interruption of the bronchial circulation

- ✓ We appreciate your valuable note. We corrected the text according to your suggestions.

Last sentence: immunosuppressive therapy: I would provide more information (e.g. high-dose corticosteroids)

- ✓ Thank you for your valuable comments. We added the additional information about immunosuppressive therapy.

Native lung - I would highlight this part more as this is specific for SLTx (compared to SSLTx). Now, I miss some more information of native lung complications, including epidemiology, other types of complications (infection/persistent colonization, malignancy in the native lung (refer to later part), influence on mortality (lower mortality in case of native lung complications)…

- ✓ We think this is an excellent remark. We have added more information about native lung complications after SLT.

Line 10: typo: treat GI - The section is in my opinion too long and especially the first part is quite vague. What kind of GI complications do the authors mean? I would mention the higher incidence of gastropareses (post-operative + due to medication), micro-aspiration, diminished cough reflex, abnormal mucociliary clearance.. this is mentioned later in the section: I would shorten this section and start with the possible GI complications (now mentioned later in the section) and causes

- ✓ Thank you for your valuable comments. We have shortened the GI part, and we have added more detailed information about the complications as you recommend.

Malignancy - Nice section in which the authors highlight the impact of the native lung after SLTx - I would mention that the carcinomas are often also more aggressive and diagnosed in a more advanced stage

- Line 21: typo: third cause of death after graft rejection and infection

- ✓ The mistake was corrected.

- The authors indeed highlight the frequency of skin tumors, I would therefore mention that regular skin checks (preferably by a dermatologist) are recommended as well as good sun protection.

- ✓ We think this is an excellent remark. We added some information about the frequency of non-melanoma skin cancer and some recommendations about these patients' follow-up.

Conclusion - Remove "the aim of this review…, we will discuss…" as it is not relevant anymore.

- ✓ Thank you for your valuable note. We corrected the text according to your suggestions.

Reviewer #2. No 03582196

Conclusion: Minor revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

The manuscript mainly elaborates an emphasis on factors leading to post-SLT complications in the early and late periods and their association with morbidity and mortality in these patients. By referring to a large number of literatures, the author comprehensively elaborated postoperative complications of SLT, including technical transplant complications, primary graft dysfunction, native lung complications and complications of various systems after transplantation, and summarized the main mechanism of postoperative complications of SLT.

- ➢ Thank you for the overall high evaluation of our paper.

The topic of this paper is focusing on factors affecting complications development and mortality after single lung transplant, but invasive fungal infections is also the main cause of morbidity and mortality in this population. Although the relationship between EBV and immunosuppression was expounded in this paper, why did the author not elaborate the infectious factors separately?

- ➢ Thank you for the excellent remark. We agree that the topic regarding infections, and especially fungal, are critical contributing factors to the overall mortality

after SLT. Our focus, however, was directed on the other factors. Nevertheless, we consider this suggestion as essential. Thus, we added some information in the section on immunosuppression.

In addition, among the 99 references cited in the manuscript, the references of the recent three years accounted for about 10%, and the references of the recent five years accounted for about 34%. It would be better if the references of the recent three years could be added appropriately.

- We agree with the referee that the cited papers for the last three or five years are a relatively small number compared to all other references. We performed an additional literature search and based some suggestions to include papers suggested by the other reviewers.

Name of journal: World Journal of Transplantation

Manuscript NO: 65395

Authors: Metodija Sekulovski, Bilyana Simonska, Milena Peruhova, Boris Krastev, Monika Peshevska-Sekulovska, Lubomir Spassov, Tsvetelina Velikova.

Dear Editor,

Dear reviewers,

Thank you for your time to revise once again our Manuscript ID: 65395, Factors affecting complications development and mortality after single lung transplant.

We took into account all the comments and suggestions made by the reviewers, and made the respective changes in the manuscript. Those changes are highlighted within the manuscript. Please see below, in blue, for a point-by-point response to the reviewers' comments.

Peer-review report Round 2

Reviewer #1: 05820375

Conclusion: Accept (General priority)

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

This is in general a well-written and nice and complete overview of early and late post-SLTx complications. The manuscript has been updated very nicely. Congratulations to the authors.

- Thank you for the high evaluation of our paper.

I only have some typos and grammar errors that best should be corrected before publication: Typos/grammar:

Thank you for the valuable comments and suggestions. They improved our paper significantly.

- Figure 1: alograft -> allograft → corrected
- ALAD-CLAD

line 9: as higher as -> as high as; → corrected

line 10: made by the transbronchial -> made by transbronchial; → corrected

line 32: for three weeks after -> three weeks after → corrected

- VTE

line 8: a part -> the part; → corrected

line 10: the efforts must be -> efforts must be, → corrected

towards their early -> towards early → towards the early

- Native line

line 1: it still is -> it is still; → corrected

regarding the native lung; → corrected

line 6: this can lead to potentially compromising both early and late outcomes -> this can potentially compromise both early and late outcomes; → corrected

line 16: spread the infection -> spread of the infection; → corrected

line 36: threat -> treat → corrected

- GI:

line 7: it was established a correlation between -> a correlation was established between; → corrected

line 12: is associated -> are associated; → corrected

line 25: include -> included; → corrected

line 44: is -> was. → corrected

Furthermore, I would put this sentence back in "Severe GI complications have been identified as any GI or biliary tract-related diagnosis leading to a significant repercussion for the patient that could endanger their life or involve an invasive therapeutic procedure [72]." as this information is essential to understand which GI complications are considered as severe.

The sentence was added.

- Kidney line 24: CIN -> CNI; it is CNI

line 25: deuteriation -> deterioration corrected

- Malignancy

line 24: It was estimated high frequency of skin cancer in a study by Mayo Clinic, among lung recipients with squamous cell and basal cell cancer incidence is 28% and 12%, respectively, within five years of LT -> a high frequency of skin cancer was demonstrated in a study by the Mayo Clinic, with an incidence of squamous cell and basal cell cancer of 28% and 12%, respectively, among lung transplant recipients; → the sentence was corrected

line 39: EBV infection and immunosuppression play a significant role in their pathogenesis. → corrected

- Conclusion: you can remove the last 4 lines as it is not relevant anymore.

  - We are very thankful for the thorough review. All of the issues have been corrected.

ROUND 1 – all of the issues were addressed

Reviewer #1 No. 05820375

Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

The manuscript by Sekulovski and colleagues is well-written and a pleasure to read, and provides a nice overview of LTx-related problems. However, since the title is "after SLTx" I do miss emphasis on the differences between SLTx and SSLTx. After all, a lot of these complications are not specific for SLTx and happen after LTx in general (cardiovascular, renal, AR/CLAD…). It would be nice to mention this, and highlight some of the differences between SLTx and SSLTx (highlight the part of native lung complications for example). (or rephrase the title to after lung transplantation in general)

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Introduction - Likewise, I would nuance the lower morbidity and mortality rates compared to SSLTx.

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- ➢ Typo line 9: because "of" Post SLTx complications related to graft function

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- Line 9: I would rephrase to "early ventilator weaning during the first 12h is recommended" PGD

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- ✓ Thank you for your comment. We have changed the sentence as you recommend.

Line 16: "have longer-term survival", would rephrase it to "have a better (long-term) survival"

- ✓ We appreciate your valuable note. We corrected the text according to your suggestions.

Regarding the risk factors for PGD, I would mention that these are possible risk factors, some of those listed are less likely to be risk factors (e.g., gender and race were not confirmed in large multicenter cohort studies) than others. I miss aspiration as possible risk factor.

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The transition "an inappropriate treatment strategy may affect long-term survival, leading to the development of CLAD" sounds a bit to straightforward, I would mention that this is because PGD is a risk factor for CLAD ("may affect long-term survival, since PGD is a risk factor for the development of CLAD").

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- ➢ Line 18: "AMR should be better diagnosed". Absolutely agree! Maybe the authors can give some comments/reasons why? Limitation of C4d staining, inter-observer variability, relevance of non-DSA HLA…

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- The information about ALAD is a bit too short in my opinion, and also not fully correct as you say is it frequently treatable with steroids – but this depends on the cause of course. I would give some examples of causes: allograft-related (e.g, AR, infection, anastomotic problems…) or non-allograft related (e.g. pleural).

✓ Thank you for your constructive comment. We added in the review relevant information about ALAD and conditions related to its development.

- Also "the diagnosis of CLAD can be assumed after 3 weeks" depends on the exclusion of underlying causes. After all, if ALAD was caused by an anastomotic stricture it is likely this will persist after 3 weeks (especially if no intervention) but this is not CLAD. "Conditions such as restriction and/or obstruction of airflow. are associated with CLAD development". It is for me not clear what the authors want to say (I assume that they want to mention that there are restrictive and obstructive forms of CLAD, but now I can interpret it that restriction due to obesity leads to CLAD). I would remove (or rephrase) this sentence.

  ✓ We accept the suggestion and revise the paragraph accordingly.

- I would use the latest CLAD definition (Verleden 2019) which does not include specific causes leading to chronic loss of allograft function – with the subdivision into BOS and RAS phenotype (and ARAD not anymore)

  ✓ We have added the proper information from the paper written by Verleden et al.

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- We agree with the referee that written in such a way, it may be misleading. Therefore, we split the sentence and add the information.

- Likewise, the authors state that 50% of SLT recipients develop CLAD but this counts for SSLTx as well. Would clarify this.

- ✓ We appreciate insightful comments. We clarified the difference between ALAD and CLAD and different types of CLAD (obstructive, restrictive, or mixed pattern). We also corrected the definition of CLAD according to the study of Verleden et al. as you suggested.

- ➢ Figure 1: you give different causes of chronic loss of allograft function but this is not the same as chronic rejection/CLAD, would rephrase the title to chronic complications or something like that.
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Technical complications - Line 9: would remove however;

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Typo: complex instead of complexed

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Associated factors: I don't fully understand the PGD example the authors are giving, I miss the most important factor "lack of perfusion" due to interruption of the bronchial circulation

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Native lung - I would highlight this part more as this is specific for SLTx (compared to SSLTx). Now, I miss some more information of native lung complications, including epidemiology, other types of complications (infection/persistent colonization, malignancy in the native lung (refer to later part), influence on mortality (lower mortality in case of native lung complications)…

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Malignancy - Nice section in which the authors highlight the impact of the native lung after SLTx - I would mention that the carcinomas are often also more aggressive and diagnosed in a more advanced stage

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- The authors indeed highlight the frequency of skin tumors, I would therefore mention that regular skin checks (preferably by a dermatologist) are recommended as well as good sun protection.

- ✓ We think this is an excellent remark. We added some information about the frequency of non-melanoma skin cancer and some recommendations about these patients' follow-up.

Conclusion - Remove "the aim of this review…, we will discuss…" as it is not relevant anymore.

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Reviewer #2. No 03582196

Conclusion: Minor revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

The manuscript mainly elaborates an emphasis on factors leading to post-SLT complications in the early and late periods and their association with morbidity and mortality in these patients. By referring to a large number of literatures, the author comprehensively elaborated postoperative complications of SLT, including technical transplant complications, primary graft dysfunction, native lung complications and complications of various systems after transplantation, and summarized the main mechanism of postoperative complications of SLT.

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The topic of this paper is focusing on factors affecting complications development and mortality after single lung transplant, but invasive fungal infections is also the main cause of morbidity and mortality in this population. Although the relationship between EBV and immunosuppression was expounded in this paper, why did the author not elaborate the infectious factors separately?

- Thank you for the excellent remark. We agree that the topic regarding infections, and especially fungal, are critical contributing factors to the overall mortality after SLT. Our focus, however, was directed on the other factors. Nevertheless, we consider this suggestion as essential. Thus, we added some information in the section on immunosuppression.

In addition, among the 99 references cited in the manuscript, the references of the recent three years accounted for about 10%, and the references of the recent five years accounted for about 34%. It would be better if the references of the recent three years could be added appropriately.

- We agree with the referee that the cited papers for the last three or five years are a relatively small number compared to all other references. We performed

an additional literature search and based some suggestions to include papers suggested by the other reviewers.