

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-48>

Reviewer A

ABO-incompatible lung transplantation is an interesting and important topic and this article summarizes the few published cases well. I think the review would benefit from a few additions:

Comment 1: Given the target audience, clearly defining ABO major and minor incompatibility in the text is important (in addition to the figure 1).

Reply 1: I appreciate the reviewer's thoughtful comment. I add some statements in the manuscript.

Changes in the text:

A major ABO incompatibility exists when a novel immunodominant sugar moiety (A: N-acetylgalactosamine; B: galactose) from a donor lung is transplanted into a recipient with the corresponding blood type antibodies (anti-A, anti-B, and anti-A, B). This clinical scenario occurs most frequently in blood type O patients who are receiving lung transplantations from blood type A, B, or AB donors. By contrast, minor ABO incompatibility most frequently occurs when a blood type O donor lung is transplanted into blood type A, B, or AB recipients. (Page 6, line 12-18)

Comment 2: Indicate that the need to explore ABO incompatible lung transplants extends beyond the long wait time for deceased donor lung transplants in Japan--describe the wait list mortality worldwide (ISHLT data), and in particular comment on the increased wait list mortality for blood type O lung transplant candidates, in whom ABOi transplants may benefit the most.

Reply 2: I appreciate the reviewer's thoughtful comments. I add some statements in the manuscript citing several references.

Changes in the text:

According to OPTN/SRTR 2020 annual data report, the median waiting time for listed candidates in the North America was shortened to be 1.4 months and waitlist mortality was 16.1 deaths per 100 waitlist years (7). By contrast ~~Furthermore~~, in Japan, where the shortage of donor organs is the severest in the world (the waiting time for cadaveric lung transplantation exceeds more than 900 days, resulting into an approximately 50% mortality rate), living-donor lobar lung transplantation (LDLLT) has been

constantly performed in addition to the aggressive use of marginal donor lungs (8). (Page 5, line 7-13)

Ref.

7. Valapour M, Lehr CJ, Skeans MA, et al. OPTN/SRTR 2020 Annual Data Report: Lung. *Am J Transplant* 2022; Suppl 2: 438-518.

8. Hiramata T, Akiba M, Watanabe T, et al. Waitlist mortality in lung transplant candidates in Japan. *Transplantation* 2022; 106: 1507-1509.

Comment 3: Further discuss the use of blood group A2 donors. Blood group A2 specifically is less immunogenic due to low level of antigen presence on the cells so they are used commonly in renal transplants for A2 to O and A2 to B transplants among candidates with low level anti-A antibody titers. This concept should be explored and described in more detail as it may be possible in lung transplantation also.

Reply 3: I appreciate the reviewer's instructive comment. I totally agree with the reviewer's comment. I add some statement in the manuscript, citing several new references.

Changes in the text:

Moreover, there are more experiences and knowledge available for ABO-incompatible lung transplantation. For example, there are two main phenotypes of blood type A, the A1 and A2, which differ in antigenicity as determined by the amount of surface antigens (31, 32). The surface of a subgroup A1 erythrocyte reportedly carries approximately one million blood type antigens, while a subgroup A2 erythrocyte displays less than one-third of that number (33), which suggests the possibility of transplanting a blood type A2 donor lung into a blood type O or B recipient. (Page 12, line 7-13)

Ref

32. Breimer ME, Molne J, Norden G, Rydberg G, Thiel G, Svalander CT. Blood group A and B antigen expression in human kidneys correlated to A1/A2/B, Lewis, and secretor status. *Transplantation* 2006; 82: 479-485.

33. Takahashi K. A new concept of accommodation in ABO-incompatible kidney transplantation. *Clin Transpl* 2005; 19 Suppl 14: 76-85.

Comment 4: Briefly discuss the use of ABOi lung transplantation in infant/pediatric transplants to be complete.

Reply 4: I appreciate your thoughtful comment. I add some statement in the manuscript. Changes in the text:

In heart transplantation, infant ABO-incompatible transplantation has been considered routine in some centers with excellent early and long-term results, which might be due

to the immature immune system in these small children (14). This fact also suggests the possibility of starting ABO-incompatible lung transplantation with infant and pediatric recipients. In the first intentional LDLLT at Kyoto University, the recipient was a pre-teen/teen age child and she received a single lobe from an ABO-incompatible donor and another lobe from an ABO identical donor, which might affect the outcome (30). (Page 12, line 13-19. Page 13, line 1)

Reviewer B

Comment: This report is significant because it shows current information about ABO Blood Type Incompatible Lung Transplantation.

The manuscript is well oriented

The graphic is informative.

Reply: Thank you so much for the reviewer's kind comments.

Reviewer C

The manuscript well summarizes the past publication of major ABO incompatible lung transplantation. Manuscript also includes excellent summary of passenger lymphocyte syndrome in minor ABO mismatch lung transplant, detailed experience of ABO mismatch lung transplantation for CLAD after HSCT in Japan, and most recent breakthrough which aimed to remove blood type A antigen expression in the donor lung with EVLP.

I have some minor comments/concerns regarding this manuscript.

Comment 1: In thoracic transplant, blood type incompatible transplant is standard practice in pediatric heart transplantation. I would recommend commenting in this point emphasizing the importance of age in blood type incompatible transplant.

Reply 1: I appreciate the reviewer's thoughtful comment. I totally agree with the reviewer's comment. I add some statement in the manuscript.

Changes in the text:

In heart transplantation, infant ABO-incompatible transplantation has been considered routine in some centers with excellent early and long-term results, which might be due to the immature immune system in these small children (14). This fact also suggests the possibility of starting ABO-incompatible lung transplantation with infant and pediatric recipients. (Page 12, line 13-17)

Comment 2: The reported successful case includes younger age (11 yo) and single lung transplant, which might affect the outcomes. It may be judicious to comment these factors on interpretation.

Reply 2: I appreciate the reviewer's instructive comment. I agree with the reviewer's comment. I add some statement in the manuscript.

Changes in the text:

In the first intentional LDLLT at Kyoto University, the recipient was a pre-teen/teen age child and she received a single lobe from an ABO-incompatible donor and another lobe from a ABO identical donor, which might affect the outcome (30). (Page 12, line 17-19. Page 13, line 1)

Reviewer D

In this review, the author, who is an expert on the field of lung transplantation reviews the given evidence on the feasibility of performing both minor and major ABO-incompatible lung transplantation which may constitute an additional source to face organ shortness.

The review is well written and summarizes all relevant references of the field furthermore providing a comprehensive overview on geographic discrepancies.

Of translational relevance, the author dissected transplant cases primarily performed in Japan in which the recipient had undergone HSCT which may alter the occurrence of ABO antibodies towards a potential major ABO-incompatible donor. This viewpoint is novel and of great interest as it is currently not implemented in international transplant guideline and may indeed - once enough evidence is given – help to compromise the gap between demand and supply in this unique transplant setting.

Minor Comment:

Since the author lists quite a range of papers reporting on smaller patient cohorts or case reports with ABO-incompatible transplantation, it would support the clarity of the manuscript to add an overview-table summarizing those references in a structured manner.

Reply: I appreciate the reviewer's thoughtful comments. I add one table as Table 1 in the manuscript.

Changes in the text: Most cases of major ABO incompatibility in lung transplantation in the world were discovered post-transplantation, and there are only a few reports of intentional transplantation (Table 1). (Page 8, line 11-13) I also add Table 1.