

Peer Review File

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Review Comments

Reviewer A

The authors describe in their manuscript the influence of the HLA genetic background on lung transplant outcome in Japan. Their thesis is that a more similar genetic background in Japan has beneficial impact on survival. They compare their results with UNOS data. The manuscript is well written.

Response: We appreciate the reviewer's positive comments.

Reviewer B

This is a nice review on the relationship between genetic background and outcome of lung transplantation. Authors did extensive manuscript search and presented a comprehensive review on this issue.

Response: We appreciate the reviewer's positive comments.

Reviewer C

The review article "Does the human leukocyte antigen relative homogeneous genetic background relate to better lung transplantation outcomes in Japan" written by Matsumoto and colleagues tried to examine if the relatively good outcomes of lung transplantation in Japan could be explained by the homogeneity of the population associated with similarity of HLA between donors and recipients in Japan. The points of discussion are unique and attractive. The conclusion is reasonable. However, there are multiple points to be improved toward publication.

In general, I wonder if the manuscript has gone through English editing. Some parts are hard to understand or misleading. For example, in the abstract (lines 3-4), they wrote "While the genetic background of the Japanese may be relatively similar to those of people from other countries". I think the authors meant "the genetic background of the Japanese may be relatively homogeneous compared with those from other countries" rather than the genetic background of Japanese people is similar to those outside of Japan.

Response: We thank the reviewer for the valuable comments. Our manuscript has indeed undergone English editing. We have re-checked the entire manuscript and revised the sections as follows:

1. Page 2, line 3: The genetic background of the Japanese may be relatively homogeneous compared with those of other countries.
2. Page 3, line 46: The genetic background may be relatively homogeneous in the Japanese people compared with people in other countries.

There are words like "Han Chinese", "Ryukyu (Okinawa)", and "Hondo", which need explanation to be better understood.

Response: We thank the reviewer for the comments. The terms pointed out by the reviewer may be difficult for readers to understand. We have added an explanation at the end of the paragraph on page 3, line 64. The sentence now reads as follows:

This was observed between seemingly homogeneous populations, such as China and Japan, including the northern and southern Han Chinese, who are an East Asian ethnic group native to China (5), the Hondo, who reside in mainland Japan, and Ryukyu Japanese, who reside on the Okinawa islands (6).

P8: They discussed about the outcomes of liver transplantation in Japan and other countries. At the end, they described “Nevertheless, it is still difficult to evaluate the outcomes of liver transplantation because the number of living donor transplantations in Japan is higher than that in other countries”.

I think this is an important point and if this was the case, it should be clarified at the beginning of the paragraph and also comparison between Japanese liver transplant and that of other countries is not reliable. Thus, the statement “According to 188 these data, the outcome of liver transplantation in Japan was worse than that in the United Kingdom and Canada. However, the overall survival in the United States and Europe is poorer than that in the United Kingdom (P8 lines 187-190).” I think this somewhat offensive statement needs to be made very carefully.

Response: We thank the reviewer for the comments. We agree with the reviewer’s opinions. Indeed, the expression could be considered offensive; however, the published data are factual. Therefore, we have changed the sentences on page 8, line 178 as follows: In terms of liver transplantation, comparing the outcomes of liver transplantations in Japan and other countries is difficult because the number of living donor transplantations in Japan is higher than that in other countries. In some previous reports, the survival rates between parts of the United Kingdom and Japan were similar. The 1-, 5-, 10-, and 20-year patient survival rates were 98%, 95%, 87%, and 62% in the United Kingdom and 100%, 96%, 88%, and 62% in Japan, respectively (21). Meanwhile, in Japan, patient survival was 89.1%, 85.2%, 82.9%, 75.4%, and 70.7% after 1 year, 3 years, 5 years, 10 years, and 15 years, respectively, following liver transplantation from cadaveric donors, and 85.0%, 80.9%, 78.5%, 73.2%, 68.5%, 65.7%, and 64.6%, after 1 year, 3 years, 5 years, 10 years, 15 years, 20 years, and 25 years, respectively, following liver transplantation from living donors. The 1-, 5-, 10- year patient survival rates were 98%, 95%, 87%, and 62% in Nottingham and 100%, 96%, 88%, and 62% in Japan, respectively (22). According to these data, we may tentatively conclude the following. The outcome of liver transplantation in Japan might be worse than that in the United Kingdom and Canada. However, the overall survival in the United States and Europe may be poorer than that in the United Kingdom (22-24). Nevertheless, it is still difficult to evaluate the outcomes of liver transplantation because the number of living donor transplantations in Japan is higher than that in other countries.

In Japan, many cases of living lung transplantation are done. I believe the donor-recipient similarity in HLA would be more than that of cadaveric lung transplantation. How are the results different and does it help to address the question of the paper?

Response: We thank the reviewer for the valuable question. This question is most important when describing the difference in lung transplant outcomes between Japan and other countries. However, living donor lung transplantation includes several factors involving the outcomes of lung transplantation in Japan. Therefore, it is difficult to describe the outcomes of lung transplantation in Japan when only considering HLA involvement in lung transplantation. Additionally, the effect of living donor lung transplantation should be described by other authors.

The conclusion is reasonable. Namely, the good outcome of Japanese lung transplantation is not easily explained by genetic homogeneity of the population. If this was a case, it would be better to discuss what kind of other factors could be involved even if they are only speculation.

Response: We thank the reviewer for the valuable comment. This review is part of the special issue titled “Why is the outcome of lung transplantation in Japan better than that in other countries?”. Thus, we expect that other articles should include other points of view. Our study only is a comparison of genetic homogeneity in the Japanese population.

Reviewer D

Recommend focusing on outcome in lung transplant

Expand discussion on known factors that impact outcome for Lung transplant.

Response: We thank the reviewer for the valuable comments. We agree with the reviewer’s suggestion. However, this mini-review is part of a special issue on Japanese transplantation. Thus, we expect that outcomes and other factors will be described by other authors, and additional details regarding the outcomes are beyond the scope of our article: we have only focused on the effects of genetic background.

Expand on discussion related to HLA homogeneity in Japan with more detail on known degree of HLA heterogeneity/homogeneity in Japan and other comparator countries.

Response: We thank the reviewer for the valuable comments. We agree with the reviewer’s opinion. However, there is a small number of studies that have described HLA homogeneity in Japan and other countries. When explaining HLA homogeneity, the discussion needs to be based on race rather than country. Furthermore, most countries where lung transplantation is performed are in Europe and North America. These countries often have different ethnic groups. Therefore, in these countries, it is difficult to describe HLA heterogeneity/homogeneity. Thus, we compared and described the racial differences rather than HLA heterogeneity/homogeneity between the countries.

Consider tables to highlight reported outcome from different previously reported data.

Response: We thank the reviewer for this suggestion. Tables would be helpful for readers to more easily understand the outcomes. However, there are only a few studies describing racial mismatch in organ transplantation. Thus, the number of studies is not enough to create a table.