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Title: Donor to recipient sizing in thoracic organ transplantation

COMMENTS TO AUTHORS

Today, organ transplantation presents a treatment modality that has the potential to save lives in complex or dire situations where all explored medical and surgical options either fail or are contraindicated. However, a transplant patient is continually battling between infection and rejection. Thus, optimizing transplant success is paramount if the patient is to be given a fighting chance at survival. This would start most obviously and initially with appropriate organ selection. Thus, the authors present an appropriate, relevant, and important review to improve the current clinical practices. That said, availability of organs is the rate-limiting step in offering this modality of treatment. And this study suggests more stringent rules be applied to the selection process, which may lead to preclusion of patients from transplantation. Therefore, the risk of organ mismatch transplantation must be weighed against the risk of non-transplantation and a clear link with transplant failure must be established to favor a change in practice favoring more stringent selection. It is important to state in the introduction that height and weight surrogates as estimates to organ size do not take gender-related differences into consideration AND that the refined pTLCratio accounts for these differences. It is found in the abstract but not stated again until the middle of the paper. It is also important to give the reader/reviewer an idea (published or theoretical) of how restrictive (or not) using the pTLCratio can be. Page 10: "Our data suggest that the secular trend to favor undersized donor lungs is ill advised. The advantage of using oversized donor lungs is supported by the pathophysiological consideration that link undersizing and oversizing to allograft function and injury patterns." - Are the authors suggesting that lung size mismatch transplantation is still warranted if oversized lungs are used? How does this relate to using the pTLCratio which argues for greater accuracy in donor-receipient selection. The first concept is more inclusive and widens the pool of donor-receipient matches; the second concept is more exclusive. Please clarify your thought process with regards to oversized organs and pTLCratios. The examples given make a good illustration of the authors' arguments, to a certain degree. One of their primary arguments in the review pertains to sex-mismatching. The reviewer is led to believe leading up to the examples that age-matched, gender-related organ mismatching will lead to an approximate 20% organ size mismatch. However, the cases illustrate a missed transplant opportunity from a female recipient (of a younger age). Clarification (earlier in the paper) is recommended on how gender-related mismatching is mitigated by using the pTLCratio and when gender mismatching does not pose a problem to LTx. The review seems to more heavily addresses lung transplantation than heart transplantation and the recommendations at the conclusion are geared towards lung transplantation. Can the authors make a stronger case for using pHM as they have done for the pTLC? If not, the authors might consider keeping the section on heart transplantation after their conclusions, i.e. as a "future directions" section.

Response – point by point:

Comment 1: This study suggests more stringent rules be applied to the selection process, which may lead to preclusion of patients from transplantation. Therefore, the risk of organ mismatch transplantation must be weighed against the risk of non-transplantation and a clear link with transplant failure must be established to favor a change in practice favoring more stringent selection. It is important to state in the introduction that height and weight surrogates as estimates to organ size do not take gender-related differences into consideration AND that the refined pTLCratio accounts for these differences. It is found in the abstract but not stated again until the middle of the paper. It is also important to give the reader/reviewer an idea (published or theoretical) of how restrictive (or not) using the pTLCratio can be.

Response 1: Thank you for bringing up this important point. On page 2 we have revised the abstract in the following way: "In this review we examine current data pertaining to size-matching in thoracic transplantation. We advocate for a change in the thoracic allocation mechanism from a height-or-weight-based strategy to a size-matching process that utilizes refined estimates of organ size. We believe that a size-matching approach based on refined estimates of organ size would optimize outcomes in thoracic transplantation without restricting or precluding patients from thoracic transplantation."

On page 4 at the end of the introduction we have added the following statement: "We believe that a size-matching approach based on refined estimates of organ size would optimize outcomes in thoracic transplantation without restricting or precluding patients from thoracic transplantation."

Comment 2: Page 10: "Our data suggest that the secular trend to favor undersized donor lungs is ill advised. The advantage of using oversized donor lungs is supported by the pathophysiological consideration that link undersizing and oversizing to allograft function and injury patterns." - Are the authors suggesting that lung size mismatch transplantation is still warranted if oversized lungs are used? How does this relate to using the pTLCratio which argues for greater accuracy in donor-reipient selection. The first concept is more inclusive and widens the pool of donor-reipient matches; the second concept is more exclusive. Please clarify your thought process with regards to oversized organs and pTLCratios.

Response 2: Thank you for bringing up this important point. We have clarified this by modifying this statement in the following way: "Our data suggest that the secular trend to favor undersized donor lungs is ill advised. The advantage of using well matched or oversized donor lungs is supported by pathophysiological consideration that link undersized and well matched or oversized to different allograft function and injury patterns."

Comment 3: The review seems to more heavily addresses lung transplantation than heart transplantation and the recommendations at the conclusion are geared towards lung transplantation. Can the authors make a stronger case for using pHM as they have done for the pTLC? If not, the authors might consider keeping the section on heart transplantation after their conclusions, i.e. as a "future directions" section.

Response 3: Thank you for bringing up this point. The conclusion for using the pHM are supported by a comprehensive study showing the impact of donor-to-recipient matching based on the pHM-ratio on survival following heart transplantation. This study was published in a leading cardiology journal and received wide coverage via press releases from the American College of Cardiology and was top story of the day on

“MedPage Today” including a video interview. Based on the high quality evidence supporting the pHM we believe a separate section on this topic, as currently in the manuscript, is warranted.