PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	International Collaboration: A Retrospective Study Examining The Survival Of Irish Citizens Following Lung Transplantation In Both The UK And Ireland
AUTHORS	Adamali HI, Judge EP, Healy D, Nolke L, Redmond KC, Bartosik W, McCarthy J and Egan JJ.

VERSION 1 - REVIEW

REVIEWER	Prof Geert M. Verleden University Hosoital Gasthuisberg Medical Director Lung Transplant Program Herestraat 49 3000 Leuven Belgium
REVIEW RETURNED	25/11/2011

THE STUDY	refernce list is rather old and can certainly be updated
GENERAL COMMENTS	This is a nice paper describing the excellent results for transplantation in MMUH. However, since these results seem too good and probably are amongst the best in the world they should be a litle bit more elaborated; It would be nice to see a survival curve of the patients transplanted in MMUH with the actual number of patients included at each year; It is clear from the figure that the 5 y survival is very high, but a couple of months later this is equal to the UK transplanted patients. Nevertheless the initial 5 y outcome seems to be a lot better. If the Irish programme has that good survival rates I would like to know their prevelance of BOS and their current immunosuppressive treatment schedule and follow up schedule. This may be paritcularly important for all other centers with less good results.

REVIEWER	Denis Hadjiliadis MD, MHS, FRCP(C) Assistant Professor of Medicine Pulmonary and Critical Care, University of Pennsylvania Associate Medical Director, Lung Transplantation Program Director, Adult Cystic Fibrosis Program 835W Gates Building Hospital of the University of Pennsylvania
REVIEW RETURNED	13/12/2011

THE STUDY	The design is appropriate, but there is low power for populations that are different; however, the authors are doing the best they can The main outcome measure is not completely clear: are they trying to show that doing transplants in Ireland is better or that small

BMJ Open: first published as 10.1136/bmjopen-2011-000605 on 28 March 2012. Downloaded from http://bmjopen.bmj.com/ on April 16, 2024 by guest. Protected by copyright.

	programs can do well? the outcomes are excellent and the authors downplay their favorable comparison with the UK results (which are also very good). beyond LAS we would like to know more about the patients and the waiting list management
RESULTS & CONCLUSIONS	I think further description of the patients is warranted
GENERAL COMMENTS	This is an interesting and well written paper about comparisons of transplants in the UK and Ireland of Irish citizens; both groups have had excellent outcomes; the authors are using LAS as a measure of disease severity The manuscript is worth publishing, for the collaboration aspects, but also for the excellent early results; however, some changes would strengthen the conclusions 1. How are the waiting lists managed? does LAS prioritize patients or is it up to the centers to decide, like in the UK? this is a significant issue, because if LAS is not relevant how carefully are its data updated? for example in the US we are very aggressive in updating PFTs and oxygen because they make a big difference; if it did not, we might not care documenting as accurately. Also how frequently are patients seen in Ireland or UK and how are communications done? do patients have to move to UK if listed there? 2. Some primary data on the patients (PFTs, O2 reqs in different groups, BMI vent status at transplant) might help define the patients a little better. Are they high, medium or low risk? 3. Minor comment: there is likely a typo on page 8; it says that survival at MMUH was calculated from listing and not transplant (this is likely wrong, am I correct?) 4. Were the waiting times between UK and Ireeland different? 5. Were the donor characteristics different? difficult to describe, but donor age and some other easy characteristics (secretions, PO2 and CXR) might help give us an idea on high vs. low risk. 6. How about recipient selection criteria? standard or extended? (i.e. walk distance, panresistant bacteria, obesity etc). Were they the same between UK and Ireland? any patients rejected at either center and then accepted at the other? How was the selection between UK and Ireland done? based on preference of patients or the centers? 7. Another minor comment: the authors say in the discussion that there need to be 15-20 transplants per year to assure adequate volume; this is up for debate and they should support or remove this statement 8. Finally, the discussion has to accept and discuss the limitations of such a study more. These comments are not to challenege the results. Any program that achieves 91% 5-year survival should be questioned and info obtained for incorporation by others (with the caveat that the numbers are small). A detailed description of its function would be useful Thanks for allowing me to review the manuscript

REVIEWER	Herve Mal, MD, PhD Service de Pneumologie et Transplantation Pulmonaire Hôpital Bichat, France I have no conflicts of interests with the present paper
REVIEW RETURNED	27/12/2011

BMJ Open: first published as 10.1136/bmjopen-2011-000605 on 28 March 2012. Downloaded from http://bmjopen.bmj.com/ on April 16, 2024 by guest. Protected by copyright.

GENERAL COMMENTS	The authors have compared the survival of Irish patients undergoing lung transplantation in the UK and in Ireland. Their data show that the Irish Lung Transplant program started in 2005 provides good survival results despite a quite low number of lung transplant performed. These survival results are even better than those observed in the UK centers and the difference is not explained by a lower severity of the patients transplanted in Ireland. Some points warrant further discussion 1) The reader would like to learn more on the expected consequences of this experience for Irish candidates to Lung Transplantation. Given the results obtained in Ireland, one could expect that Irish patients will not be allowed to be transplanted in the UK. 2) The survival rate of patients on waiting list is 42% but the number of patients placed on waiting list during the study periods should be given. Even if the survival results postransplant at the MMUH Dublin are good, it seems that many patients die on waiting list, suggesting that the system is not very effective. Furthermore what is the respective probability for Irish patients to be transplanted either in Ireland or in the UK once on waiting list. The authors should discuss this point. 3) table 2. Concerning the LAS score, it is not clear why it has been calculated in only 54 of the 70 CF patients

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIWERS COMMENTS

Reviewer: Prof Greet M. Verleden
University Hosoital Gasthuisberg
Medical Director Lung Transplant Program
Herestraat 49
3000 Leuven
Belgium

Reference list is rather old and can certainly be updated

RESPONSE:

We have included

De Vleeschauwer S, Van Raemdonck D, Vanaudenaerde B, Vos R, Meers C, Wauters S, Coosemans W, Decaluwe H, De Leyn P, Nafteux P, Dupont L, Lerut T, Verleden G. Early outcome after lung transplantation from non-heart-beating donors is comparable to heart-beating donors. J Heart Lung Transplant. 2009; 28:380-7.

Horai T, Shigemura N, Gries C, Pilewski J, Bhama JK, Bermudez CA, Zaldonis D, Toyoda Y. Lung Transplantation for Patients With High Lung Allocation Score: Single-Center Experience. Ann Thorac Surg. 2011 Dec 20.

This is a nice paper describing the excellent results for transplantation in MMUH. However, since

BMJ Open: first published as 10.1136/bmjopen-2011-000605 on 28 March 2012. Downloaded from http://bmjopen.bmj.com/ on April 16, 2024 by guest. Protected by copyright.

these results seem too good and probably are amongst the best in the world they should be a little bit more elaborated; It would be nice to see a survival curve of the patients transplanted in MMUH with the actual number of patients included at each year; It is clear from the figure that the 5 y survival is very high, but a couple of months later this is equal to the UK transplanted patients. Nevertheless the initial 5 y outcome seems to be a lot better.

RESPONSE:

We have now incorporated the actual numbers for MMUH for each year in Figure 2

We agree with Prof Verledens comment, consequently in the results we have emphasized the death of one patient (1 rip from liver cirrhosis) beyond 5 years which brings the survival closer to the UK after the 5 year threshold, (page 14 para 2, Figure 2)

If the Irish programme has that good survival rates I would like to know their prevalence of BOS and their current immunosuppressive treatment schedule and follow up schedule. This may be particularly important for all other centers with less good results.

RESPONSE: We have included a section on immuosuppression see page 8 and also reference to the number of patients who experienced BOS (page 14, para 2)

Reviewer: Denis Hadjiliadis MD, MHS, FRCP(C)
Assistant Professor of Medicine
Pulmonary and Critical Care, University of Pennsylvania
Associate Medical Director, Lung Transplantation Program
Director, Adult Cystic Fibrosis Program
835W Gates Building
Hospital of the University of Pennsylvania

The design is appropriate, but there is low power for populations that are different; however, the authors are doing the best they can
The main outcome measure is not completely clear: are they trying to show that doing transplants in Ireland is better or that small programs can do well? the outcomes are excellent and the authors downplay their favorable comparison with the UK results (which are also very good). beyond LAS we would like to know more about the patients and the waiting list management

I think further description of the patients is warranted

This is an interesting and well written paper about comparisons of transplants in the UK and Ireland of Irish citizens; both groups have had excellent outcomes; the authors are using LAS as a measure of disease severity

The manuscript is worth publishing, for the collaboration aspects, but also for the excellent early results; however, some changes would strengthen the conclusions

1. How are the waiting lists managed? does LAS prioritize patients or is it up to the centers to decide, like in the UK? this is a significant issue, because if LAS is not relevant how carefully are its data updated? for example in the US we are very aggressive in updating PFTs and oxygen because they make a big difference; if it did not, we might not care documenting as accurately.

RESPONSE: LAS is not used in a fashion similar to the USA. The transplant center has clinical discretion in selecting the recipients. However the LAS was accurately estimated, post hoc at the time

BMJ Open: first published as 10.1136/bmjopen-2011-000605 on 28 March 2012. Downloaded from http://bmjopen.bmj.com/ on April 16, 2024 by guest. Protected by copyright.

of transplant to bench mark the recipient population as discussed later.

Also how frequently are patients seen in Ireland or UK and how are communications done? do patients have to move to UK if listed there?

RESPONSE: Patients on the UK list are reviewed by the UK team in Ireland every 4 months. On the night of transplant patients are transported by air ambulance to the UK.

2. Some primary data on the patients (PFTs, O2 reqs in different groups, BMI vent status at transplant) might help define the patients a little better. Are they high, medium or low risk?

RESPONSE: This is an interesting point which we agree with and highlights how risk stratification should inform the interpretation of center outcomes. We believe LAS is a useful mechanism to try and bench mark recipient complexity as it has been shown to influence outcome post transplant. See reference 4

All the patients had a BMI < 28. We confer considerable importance to this variable as it is potentially a useful surrogate of rehabilitation status. Page 11, para 1

3. Minor comment: there is likely a typo on page 8; it says that survival at MMUH was calculated from listing and not transplant (this is likely wrong, am I correct?).

RESPONSE: This refers to wait list mortality

4. Were the waiting times between UK and Ireland different?

RESPONSE: No

5. Were the donor characteristics different? difficult to describe, but donor age and some other easy characteristics (secretions, PO2 and CXR) might help give us an idea on high vs. low risk.

RESPONSE: Extended detail in regards donor characteristics were not available to us. However Irish patients did not receive marginal lungs. We highlight this in the discussion (page 17, para 2)

6. How about recipient selection criteria? standard or extended? (i.e. walk distance, panresistant bacteria, obesity etc).

RESPONSE: Standard selection criteria applied.

Were they the same between UK and Ireland? any patients rejected at either center and then accepted at the other? No

How was the selection between UK and Ireland done? Based on preference of patients or the centers?

RESPONSE: Patient preference determined center selection.

7. Another minor comment: the authors say in the discussion that there need to be 15-20 transplants per year to assure adequate volume; this is up for debate and they should support or remove this statement

RESPONSE: We have removed this statement

BMJ Open: first published as 10.1136/bmjopen-2011-000605 on 28 March 2012. Downloaded from http://bmjopen.bmj.com/ on April 16, 2024 by guest. Protected by copyright.

8. Finally, the discussion has to accept and discuss the limitations of such a study more. These comments are not to challenge the results. Any program that achieves 91% 5-year survival should be questioned and info obtained for incorporation by others (with the caveat that the numbers are small).

RESPONSE: We agree with this important point and hence wish to publish the outcomes for critical appraisal in order to trigger debate in regard comparing center outcome. The intention to treat analysis emphasizes the weakness in regard to the excellent outcomes we report.

A detailed description of its function would be useful

Thanks for allowing me to review the manuscript

Reviewer: Herve Mal, MD, PhD
Service de Pneumologie et Transplantation Pulmonaire
Hôpital Bichat, France

I have no conflicts of interests with the present paper

The authors have compared the survival of Irish patients undergoing lung transplantation in the UK and in Ireland. Their data show that the Irish Lung Transplant program started in 2005 provides good survival results despite a quite low number of lung transplant performed. These survival results are even better than those observed in the UK centers and the difference is not explained by a lower

Some points warrant further discussion
1) The reader would like to learn more on the expected consequences of this experience for Irish candidates to Lung Transplantation. Given the results obtained in Ireland, one could expect that Irish patients will not be allowed to be transplanted in the UK.

RESPONSE: Prof Mal is correct based on this data the service level agreements are now ceased however Irish patients will still link with UK programs in the event of requiring additional expert opinion or treatment.

2) The survival rate of patients on waiting list is 42% but the number of patients placed on waiting list during the study periods should be given. Even if the survival results postransplant at the MMUH Dublin are good, it seems that many patients die on waiting list, suggesting that the system is not very effective. Furthermore what is the respective probability for Irish patients to be transplanted either in Ireland or in the UK once on waiting list. The authors should discuss this point.

RESPONSE: This is a very important point with which the authors agree. Simple post transplant survival data (which is the international standard) does not give a complete picture. Consequently we have now included an intention to treat analysis which we believe enhances the appraisal of our data. In essence it indicates the treatment (transplant) utility is limited because of the mortality on the waiting list. This is expanded upon in the manuscript (pages 9, 14, 16; Figure 2)

3) table 2. Concerning the LAS score, it is not clear why it has been calculated in only 54 of the 70 CF patients.

RESPONSE: In order to be accurate LAS data had to be available on the day of transplant. Accurate real time data on 16 CF patients were not available and therefore accurate data 54 patients were analyzed (page 9, para3)

BMJ Open: first published as 10.1136/bmjopen-2011-000605 on 28 March 2012. Downloaded from http://bmjopen.bmj.com/ on April 16, 2024 by guest. Protected by copyright.

VERSION 2 – REVIEW

REVIEWER	Denis Hadjiliadis MD, MHS, FRCP(C) Assistant Professor of Medicine Pulmonary and Critical Care, University of Pennsylvania Associate Medical Director, Lung Transplantation Program Director, Adult Cystic Fibrosis Program 835W Gates Building Hospital of the University of Pennsylvania
REVIEW RETURNED	30/01/2012

GENERAL COMMENTS	The authors have addressed the points raised to the best of their abilities

REVIEWER	prof GM Verleden university Hospital Gasthuisberg Lung Transplant Unit Leuven, Belgium
REVIEW RETURNED	03/02/2012

GENERAL COMMENTS	The authors have clearly responded to my concerns, therefore I have no further remarks.

BMJ Open: first published as 10.1136/bmjopen-2011-000605 on 28 March 2012. Downloaded from http://bmjopen.bmj.com/ on April 16, 2024 by guest. Protected by copyright.