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International collaboration: a retrospective study examining the survival of Irish citizens following lung transplantation in both the UK and Ireland

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ABSTRACT

Objective: Prior to 2005, Irish citizens had exclusively availed of lung transplantation services in the UK. Since 2005, lung transplantation has been available to these patients in both the UK and Ireland. We aimed to evaluate the outcomes of Irish patients undergoing lung transplantation in both the UK and Ireland.

Design: We retrospectively examined the outcome of Irish patients transplanted in the UK and Ireland. Lung allocation score (LAS) was used as a marker of disease severity.

Results: A total of 134 patients have undergone transplantation. 102 patients underwent transplantation in the UK and 32 patients in Ireland. In total, 52% were patients with cystic fibrosis, 19% had emphysema and 15% had idiopathic pulmonary fibrosis. In Ireland, 44% of the patients suffered from idiopathic pulmonary fibrosis, 31% had emphysema and 16% had cystic fibrosis. A total of 96 double sequential transplants and 38 single transplants have been performed. LAS of all patients undergoing lung transplantation was 37.8 (±1.02). The mean LAS for patients undergoing lung transplantation in Ireland was 44.7 (±3.1), and 35 (±0.4) for patients undergoing lung transplantation in the UK ($p<0.05$). The 5-year survival of all Irish citizens who had undergone lung transplantation was 73%. The 5-year survival of Irish patients transplanted in the UK was 69% and in Ireland was 91% and 73% at 5.01 years.

Conclusions: International collaboration can be achieved, as evidenced by the favourable outcomes seen in Irish citizens who undergo lung transplantation in both the UK and Ireland. Irish citizens undergoing lung transplantation in Ireland have a higher LAS score. Despite excellent outcomes, an intention-to-treat analysis of the treatment utility (transplant) indicates the limited effectiveness of lung transplantation in Ireland and emphasises the need for increased rates of lung transplantation.

ARTICLE SUMMARY

Article focus

- Determine the survival outcomes following lung transplantation for Irish patients undergoing lung transplantation in experienced UK programmes and a newly established transplant programme in Ireland.
- Compare recipient lung allocation scores (a marker of disease severity) between programmes.

Key messages

- International collaboration for complex medical services can be achieved, as demonstrated by the favourable outcomes seen in Irish citizens who undergo lung transplantation in both in the UK and Ireland.
- Irish citizens undergoing lung transplantation in Ireland have a higher LAS (44.7 (±3.1) vs 37.8 (±1.02)), suggesting that local services can accommodate patients with a greater disease burden.
- Despite excellent outcomes, an intention-to-treat analysis of the treatment utility (transplant) indicates the limited effectiveness of lung transplantation in Ireland and emphasises the need for increased rates of lung transplantation.

Strengths and limitations of this study

- This study is unique in that it gives insight into an Anglo-Irish collaboration delivering a successful highly complex service to severely ill patients. It shows excellent outcomes and offers a platform on which further development may result in increase levels of transplant activity benefiting both Ireland and the UK. A limitation of the study is the modest number of lung transplants in Ireland.

INTRODUCTION

Lung transplantation was developed in the 1980s to provide a treatment for advanced lung diseases, including cystic fibrosis (CF),

emphysema and idiopathic pulmonary fibrosis (IPF). From the years 1990 to 2000, lung transplantation was available in the UK for Irish patients who were selected and referred on an ad hoc basis by individual physicians. In 2000, the Irish Department of Health and Children (DOHC) formally commissioned and funded a service-level agreement with the Freeman Hospital in Newcastle, UK, to provide lung transplantation for Irish patients. In 2005, a new clinical service providing lung transplantation was initiated at the Mater Misericordiae University Hospital (MMUH), Dublin, Ireland. In addition to being a significant step-forward for the provision of healthcare services in Ireland, it was also a unique development as the majority of national lung transplant programmes had been initiated in the years between 1985 and 1990. Therefore, the newly commissioned programme in Ireland was required to provide a lung transplant service to Irish patients in a manner that was already available in long established successful lung transplant programmes in the UK.

The aims of this study were therefore to determine the survival outcomes following lung transplantation for Irish patients undergoing lung transplantation in the UK and Ireland and to benchmark these for disease severity.

MATERIALS AND METHODS

Study population

Data from the National Lung Transplant Unit Database at MMUH were examined from 2000 to 2011. Irish citizens transplanted in the MMUH, the Freeman Hospital in Newcastle, UK, Harefield Hospital in Middlesex, UK, and Great Ormond Street in London were included in the study. Chart records of all patients who had undergone lung transplantation were examined. Demographic variables including age, gender, race, waiting-list time and primary diagnosis were documented. Patients received centre-specific immunosuppression. In the MMUH, patients received basiliximab induction therapy followed by triple therapy, including mycophenolate mofetil, tacrolimus and steroids.

Calculation of lung allocation score (LAS)

LAS was used as a measure of disease severity.[1 2] LAS values for patients were calculated using the Organ Procurement and Transplantation Network calculator. The LAS immediately prior to lung transplantation was used. The LAS score included the diagnosis of the patient (eg, emphysema, CF, etc), age of the patient, body mass index, presence or absence of diabetes mellitus, ability to function according to the New York Heart Association Scale, percentage of predicted forced vital capacity, systolic pulmonary artery (PA) pressures, mean PA pressures, pulmonary capillary wedge pressure, flow rate of supplemental oxygen required at rest, 6-min walk test, need or lack of need for continuous mechanical ventilation and levels of creatinine in the blood. Organ Procurement and Transplantation Network default haemodynamic values for systolic PA pressures, mean PA pressures and pulmonary capillary wedge pressure were entered into the LAS calculation if the value was missing.

LAS scores for each patient were calculated on clinical information relating to the immediate pre-lung transplantation period.

Sixteen patients with CF did not have real-time pre-transplant data, and therefore, the LAS score was analysed in the 54 patients with CF.

Survival analysis

Survival time for Irish citizens who underwent lung transplantation in the UK and at the MMUH, Dublin, was calculated from the time of lung transplant to the time of death or to the censoring of data on 1 March 2011.

Survival time for patients awaiting transplantation in MMUH was calculated from time of listing for lung transplantation to the time of death or to the censoring of data on 1 March 2011. Survival analysis was performed using the Kaplan–Meier and log-rank tests.

An intention-to-treat analysis of all patients who were listed for transplantation in Ireland was performed to estimate treatment effectiveness. This was performed by calculating the survival of all patients listed for transplantation. It combined the survival times of those who died awaiting transplantation and those who received a transplant.

Statistical analysis

Normally distributed data were presented as means (±SEM). Statistical comparisons of means were made using analysis of variance. For non-normally distributed data, two group comparisons of the means were made using the Mann–Whitney U test and Kolmogorov–Smirnov two-sample tests. A value of $p<0.05$ was accepted as statistically significant.

The log-rank test was used to examine survival differences. The statistical software SPSS (V.18) was used for all analyses.

RESULTS

Patient characteristics

A total of 134 Irish citizens have undergone lung transplantation. To date, 52% of transplanted patients suffered from CF, 19% had emphysema and 15% had IPF. The remaining 13% of patients had a variety of diagnoses, including lymphangioleiomyomatosis, bronchiectasis, sarcoidosis, Eisenmenger's syndrome and primary pulmonary hypertension. A total of 96 double sequential lung transplants and 38 single transplants have been performed (table 1). Fifty-one per cent of lung transplant recipients were male. There was no statistical difference between baseline characteristics of male and female patient groups. The mean age of patients with CF was 26.1 (±1) years, patients with emphysema was 53.7 (±1.3) years and patients with idiopathic pulmonary fibrosis (IPF) was 56.3 (±1.4) years.

Between 2005 and 2011, 32 patients had undergone transplantation at the MMUH, Dublin. There were 17 male and 15 female patients. Compared to the UK,

Table 1 Patient characteristics

Disease	Total number	Male/female	Lung Tx	Tx centres
Cystic fibrosis	70	38/32	70 D	5M, 59N, 4H, 2G
Emphysema	25	11/14	11D, 14S	10M, 14N, 1H
Idiopathic pulmonary fibrosis	20	13/7	3D, 17S	14M, 5N, 1H
Lymphangioleiomyomatosis	3	0/3	1D, 2S	1M, 2N
Bronchiectasis	6	4/2	5D, 1S	1M, 4N, 1H
Sarcoidosis	5	1/4	2D, 3S	1M, 4N
Eisenmenger's syndrome	2	1/1	1D, 1S	2N
Primary pulmonary hypertension	3	1/2	3D	3N
Total	134	69/65	96D, 38S	32M, 93N, 7H, 2G

The disease subtype, total number of transplants performed, male to female distribution, double (D) or single (S) transplants (Tx) and the number of transplants performed within the respective centre (M, Mater; N, Newcastle; H, Harefield and G, Great Ormond Street) are shown.

a higher proportion (44%) of these patients suffered from IPF, while 31% had emphysema, 16% had CF and equal number of the remainder of patients had lymphangioleiomyomatosis (3%), sarcoidosis (3%) and bronchiectasis (3%) (refer to table 1). The mean age of patients with CF was 28.0 (±3.1) years, patients with emphysema was 57.1 (±1.4) years and patients with IPF was 58.1 (±1.4) years. All patients had a BMI<28.

Patients with IPF on the active transplant list waited 1.05 (±0.23) years for transplantation, patients with CF waited 1.09 (±0.13) years and patients with emphysema awaited 1.65 (±0.28) years. There was no statistical difference in waiting times in the different disease groups.

Lung allocation scores

The mean LAS of all Irish citizens undergoing lung transplantation was 37.8 (±1.02) (table 2). The mean LAS for patients undergoing lung transplantation in MMUH was 44.7 (±3.1), which was significantly greater than the mean LAS (35.0±0.4) for Irish citizens undergoing lung transplantation in the UK ($p<0.05$) (table 2, figure 1). The mean LAS of all patients with IPF was 51.0 (±3.5). LAS for patients with IPF transplanted in MMUH was significantly greater ($p<0.05$) than those transplanted in the UK centres.

Survival

The 5-year survival of all Irish citizens who underwent lung transplantation (n=134) was 73% (figure 2). The 5-year survival of Irish patients transplanted in the UK centres (n=102) was 69%. The 5-year survival of Irish citizens undergoing lung transplantation in MMUH, Dublin (n=32) was 91% (with the use of log-rank test, MMUH vs UK centres, $p<0.05$). One patient died from liver cirrhosis after 5.01 years bringing the MMUH survival to 73%. This was closer to the UK survival curve at 5 years (figure 2).

Of those patients awaiting lung transplantation, the median estimates of survival was 1.3 years (95% CI 0.6 to 2.0). IPF was the leading cause of death. There was a clear survival benefit with transplantation (with the use of log-rank test, $p<0.001$). Three patients experienced bronchiolitis obliterans syndrome within 5 years of transplantation, of whom two died.

Intention-to-treat analysis

The intention-to-treat analysis showed a significantly reduced survival when compared to standard post-transplant survival ($p<0.001$) (figure 2).

DISCUSSION

All Irish citizens who underwent lung transplantation in both the UK and Ireland experienced a significant survival benefit. This study indicates that a newly commissioned lung transplant programme can deliver quality outcomes comparable to and exceeding the international averages. Patients undergoing lung

Table 2 Disease subtypes and LAS

	All centres		UK centres		MMUH	
Disease	LAS	n	LAS	n	LAS	n
Cystic fibrosis	35.2±0.3	54	35.4±0.3	49	33.1±0.7	5
Emphysema	32.4±0.4	25	32.1±0.7	15	32.9±0.4	10
Idiopathic pulmonary fibrosis	51.0±3.5	20	40.5±1.57	6	55.5±4.5*	14
Lymphangioleiomyomatosis	35.1±0.8	3	35.5±1.7	2	34.2	1
Bronchiectasis	34.5±1.3	3	33.2±0.4	2	37.2	1
Sarcoidosis	48.6±13.6	4	35.1±2.9	3	88.9	1
Eisenmenger's syndrome	28.6	1	28.6	1	–	–
Total	37.8±1.02	110	35.0±0.4	78	44.7±3.1*	32

*Significant difference between LAS of patients transplanted in MMUH and LAS of patients transplanted in UK centres ($p<0.05$).
Disease subtypes and average LAS (±SEM) in all centres, UK centres and MMUH are shown. The number of patients used to calculate each LAS is shown in each disease subtype.
LAS, lung allocation score; MMUH, Mater Misericordiae University Hospital.

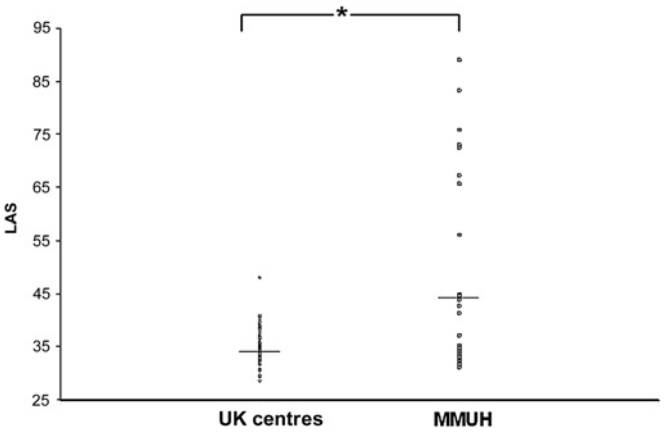

Figure 1 Lung allocation scores (LAS). MMUH, Mater Misericordiae University Hospital. Mean bar is shown. *p<0.05.

transplantation in Ireland have a 5-year survival of 91% compared to 69% in the UK and 60% internationally.[3] These favourable outcomes do not appear to be the result of selecting 'easier' cases. LAS, a surrogate of disease severity, was significantly higher in patients undergoing lung transplantation in Dublin compared to Irish patients undergoing lung transplantation in the UK. This indicates that the provision of local services may facilitate the delivery of care to higher risk cases.[4] In Ireland, although transplantation provided a survival advantage to those who received the treatment, its overall effectiveness was undermined by the high mortality on the waiting list, as demonstrated by the

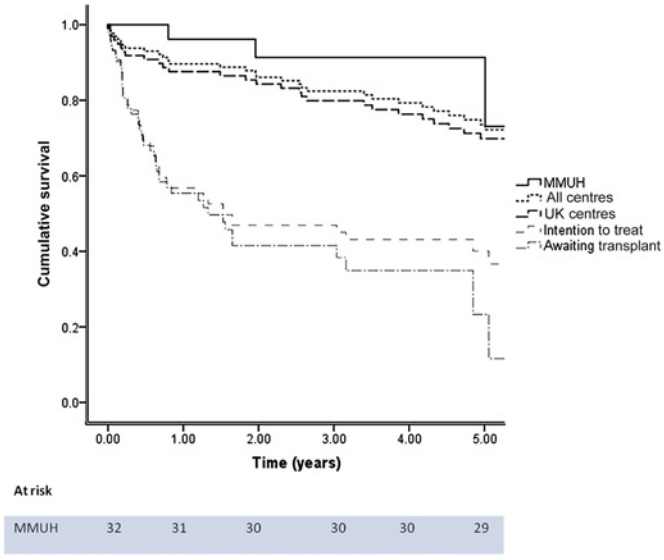

Figure 2 Survival curve of Irish patients. Kaplan–Meier survival curves of patients transplanted in Mater Misericordiae University Hospital (MMUH), patients transplanted in UK centres, combined all centres survival (UK centres and MMUH) and Irish patients awaiting transplant in Ireland. Intention-to-treat analysis evaluating treatment effectiveness demonstrates a significantly poorer survival compared to post-transplant survival (with the use of log-rank test, p<0.0001).

intention-to-treat analysis. Prior to 2000, Irish patients requiring lung transplantation were referred by paediatric and adult respiratory physicians on an ad hoc basis to any one of five centres in the UK. In the 1990s, there were approximately 22–24 Irish patients awaiting transplantation in the UK annually, with an average of one patient receiving a lung transplant annually. The response from the DOHC in Ireland was to commission a transplant programme at the MMUH, Dublin. This programme was planned and developed in a coherent logical way and commenced by linking with a centre (Freeman Hospital Newcastle) in the UK. This 'buddy' strategy was underpinned by a financial contract from the DOHC to ensure Irish patients underwent treatment. The provision of local services in Dublin was then progressed in three phases. The first stage that commenced in May 2002 involved the deployment of dedicated services for the assessment and medical follow-up of patients who had undergone lung transplantation. The second phase involved the development of a waiting list of Irish patients who wished to undergo lung transplantation in Dublin. This took 3 years and culminated in the first lung transplant being successfully performed in May 2005. The next step involved the selection of patients who required a double lung transplant, and this was performed in January 2006. This then prompted the selection of patients with CF for lung transplantation culminating in the first double lung transplant for CF being performed in July 2007. Based on the favourable data set, only patients with unusually complex needs will travel to the UK for services. However, because of the links between the UK and Ireland, two common misconceptions emerged. The first of these was that Irish patients can be on both the Irish and the UK waiting lists at the same time. This is not possible because such an arrangement may result in a subset of patients being treated more favourably. The second misconception is that the UK services guarantee a transplant and the Irish system does not. Regrettably, the mortality of patients awaiting lung transplantation is likely to be comparable in both services. Indeed, the mortality for the subset of patients with IPF approaches 50%. Consequently, the core challenge for the emerging Irish programme is to increase the quantity of transplants.

An annual transplant rate of six to eight per annum in Ireland is modest, and it is recognised that 'small volume' programmes are associated with an increased risk of mortality following transplantation. However, a recent study also indicated that 'small volume' programmes can have excellent outcomes.[5] That study highlights an additional variable of a 'centre effect'. Individual programmes despite the volume activity can deliver favourable outcomes when compared to 'large volume' programmes.

In Ireland, although transplantation provided a survival advantage to those who received the treatment, its overall effectiveness was undermined by the high

mortality on the waiting list. Although the outcomes following transplantation are excellent, the intention-to-treat analysis emphasises the critical need for greater numbers of transplants. The required increase in quantity of lung transplantation presents a complex challenge that demands overall system changes within the Irish health service. Ireland has been the only European country that did not have a specific transplant organisation prior to 2010. In 2010, the European Directive for organ transplantation has stated that each jurisdiction must have a specific transplant organisation, which is responsible for audit, registration of donors, safety from infectious complications and the governance of transplant activity.[6] These issues are now currently being addressed by a newly constituted National Organ Donation and Transplantation office within the Irish Health Service Executive.

At the MMUH only those donors who fulfilled the recommended International Society of Heart Lung Transplantation criteria for donation were selected. Marginal lungs were not used. Both Ireland and the UK have among the lowest lung utilisation rates in Europe.[5] Organ care programmes in Canada and Australia have resulted in increased quantity of lung transplants.[7 8] In Ontario in particular, such strategies have resulted in a radical increase of the number of lungs used from 15% to 55%. Cadaveric lobar transplantation, ex vivo lung perfusion of marginal donor lungs and donation after cardiac death can increase the quantity of organ donors.[9 10] In the event that similar processes can be deployed in the Irish health service, it is probable that the quantity of lung transplants per annum will be enhanced, potentially resulting in a greater capacity to share organs across the UK and Ireland.

In conclusion, our data indicate favourable outcomes for Irish citizens undergoing lung transplantation in both the UK and Ireland. Furthermore, prospective planning with international collaboration allows the successful delivery of complex high-end services to patients.

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Contributors HIA examined the data and compiled this work. EPJ was actively involved in the writing of the manuscript. DH, LN, KCR, WB and JMcC (Surgical Director) are surgeons involved in the management of the patients and evaluation and writing of the manuscript. JJE is the Medical Director and was involved in the pre- and post-management of all the transplanted patients and conception of the study, interpretation of the data and writing of the manuscript.

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Data sharing statement A database exists in the Mater Misericordiae University Hospital that contains both lung and heart transplants. This is not an open database and access can be obtained through the Transplant Program Medical Director.

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