Follow up of Icelandic and Swedish Lung Transplant Patients

in the years 2010–2012

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Abstract

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Follow up and comparison of Icelandic and Swedish Lung Transplant Patients

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Introduction

Lung transplantation is a valid treatment for end stage lung disease. The most common indication is chronic obstructive pulmonary disease and the second is idiopathic pulmonary fibrosis. There is a thorough process before a patient receives a lung transplantation. First, the patient has to be referred to a lung transplant center. Then, the patient needs to be placed on the lung transplant list. The two most important things to look at before a patient is put on the transplant list are (1) will he survive the surgery and (2) how long will he survive after the surgery. There are numerous problems that lung transplant patients face. These problems arise from the medication and rejection of the lung allograft. The treatment is centered on immunosuppression with the aim of delaying the development of BOS. The treatment is also aimed at reducing the occurrence of factors that increase the likelihood of developing BOS, such as CMV infection and acute infection.

Methods and material

Information from 10 Icelandic patients and 20 Swedish patients was collected at the National Hospital of Iceland and at Sahlgrenska University Hospital in Sweden. The information collected included four years of follow up and the values before the transplant for lung function and plasma clearance. Additional information collected included the number of patients with BOS, occupation, different types of lungs received, CMV status, survival, how many received a CMV treatment, and how many CMV treatments were prescribed.

Results

Looking at the follow up of lung function and kidney function, the patients seem to be stable and doing well. There is a major increase in lung function values after the surgery, but after that the patients have relative constant lung function values, on average. In comparing the patient groups for lung function, there was one major difference—Sweden was doing much better. Iceland had a higher rate of survival than Sweden, but Iceland had higher levels of BOS.

Conclusion

Both patient groups seem to be benefitting from the transplants, since both groups have an average increase in the lung function values FEV1 and FVC and on average do not have a clinical manifestation of kidney disease according to the plasma clearance levels. The main difference between Iceland and Sweden was the difference in lung function values; this seems to have occurred because Sweden‘s COPD patients received larger lungs than Iceland‘s COPD patients; however, the difference in reference values also plays a part. The sample population evaluated for this study was very small, so any difference in the two patient groups requires further research.

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Abbreviations

AATD	Alpha-1 antitrypsin deficiency
BMD	Bone mineral density
BO	Bronchiolitis obliterans
BOS	Bronchiolitis obliterans syndrome
CF	Cystic fibrosis
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
COPD/COPD	Comparing Sweden's and Iceland's COPD groups
COPD/non-COPD	Comparing Sweden's COPD group to Iceland's non-COPD
CPFE	Combined pulmonary fibrosis and emphysema
EVLP	Ex-vivo lung perfusion
FEV1	Forced expiratory volume in one second
FEV1%	Forced expiratory volume in one second percentage
FVC	Forced vital capacity
FVC%	Forced vital capacity percentage
GVH	Graft versus host disease
Iceland c.	Iceland corrected
IPF	Idiopathic pulmonary fibrosis
l	Liter
LAM	Lymphangioleiomyomatosis
LTR	Lung transplant recipients
LTx	Lung transplant
min	Minute
ml	milliliters
Non-COPD/COPD	Comparing Sweden's non-COPD group to Iceland's COPD
Non-COPD/non-COPD	Comparing Sweden's and Iceland's non-COPD groups
PAH	Pulmonary arterial hypertension
PCP	Pneumocystis pneumonia
PGD	Primary graft dysfunction
PTLD	Post transplant lymphoproliferative disease
RAS	Restrictive allograft syndrome

RA. bronchiolitis	Bronchiolitis as a part of rheumatoid arthritis
ReTx	Retransplantation
SL	Single lung transplant
SLE	Systemic lupus erythematosus
TLC baseline	Total lung capacity baseline
DL	Double lung transplant
D+/R+	CMV status, when the donor is CMV seropositive and the recipient is CMV seropositive
D+R/-	CMV status, when the donor is CMV seropositive and the recipient is CMV seronegative
D-/R+	CMV status, when the donor is CMV seronegative and the recipient is CMV seropositive
D-/R-	CMV status, when the donor is CMV seronegative and the recipient is CMV seronegative
0 to 1	Stands for the change in spirometric values from before the surgery until the first year of follow up.
1 to 2	Stands for the change in spirometric values from the first year of follow up until the second year of follow up.
2 to 3	Stands for the change in spirometric values from the second year of follow up until the third year of follow up.
3 to 4	Stands for the change in spirometric values from the third year of follow up until the fourth year of follow up.

1 Introduction

1.1 Brief history of lung transplantation

Lung transplantation is a life saving procedure that is a part of the success of modern medicine. In 1963, after testing lung transplantation and immunosuppressant therapy on 400 dogs, Dr. James Hardy performed the first human lung transplant. The surgery went well but the patient died 18 days after the surgery [1].

In the ensuing 10 years, only 36 transplants were performed worldwide. Survival was only a few days in most cases, and only two patients survived for more than a month [1]. The leading cause of death was poor healing of the airway anastomosis, caused by the overuse of steroids. However, this all changed in 1981, when the use of cyclosporine reduced the amount of steroids needed for immunosuppression [1]

Dr. Norman Shumway and his colleagues used cyclosporine after performing three heart-lung transplants in 1981, two of the patients were alive when the doctors published their article in 1982 [1]. Since then, the number of transplants has increased every year. In 1987 there were 45 transplants, while in 1990 this quantity had risen to 400. It kept increasing until the 1990s, when it hit a temporary ceiling of 1400 performed every year [1]. Today it has risen to more than 3000 per year [2].

1.2 History of lung transplantation in Icelandic patients

The first lung transplant for an Icelandic patient was performed in 1988. There have been a total of 22 Icelandic lung transplant recipients from 1988 to 2015. Iceland has twice had a contract with Sahlgrenska University Hospital in Gothenburg, Sweden concerning organ transplantation of Icelandic citizens. The first period from 1990 to 2000 and the second from 2010 to 2020. In between these two periods, Iceland had a contract with Denmark lasting from 2000 to 2010. The first and the second lung transplantation performed on Icelandic patients were performed in Harefield hospital in London.

During the first contract period with Sweden, there were four lung transplants performed in Gothenburg at the Sahlgrenska University Hospital. During this time in 1992 there was one transplant performed in the United Kingdom. In 2000, Iceland decided to change the transplant contract to Denmark. During the contract period with Denmark, four lung transplantations were performed and one patient died on the transplant list.

In 2010, the contract was moved back to Sahlgrenska, Sweden. In the first five years of the second contract period with Sweden, there have been 11 lung transplants performed on Icelanders. Ten of these lung transplants were performed in the first three years. In the same time period, there was one patient who got a lung transplant in the USA. From 2010 to 2012 there was a high transplant frequency compared to the period while Iceland had a contract with Denmark. Since then, there has been one transplant, performed in 2014. Two patients are currently on the waiting list. One is going to undergo a re-transplantation. This is a frequency to be expected based on the numerically small Icelandic population, approximately one patient per year.

1.3 The cost of lung transplantation

Transplanting a lung is very expensive and should be cost-effective compared to other treatment options, survival, and quality of life. The reason why the cost of a lung transplant is not the focal point of lung transplantation is that transplantable lungs are a scarce resource. Double lung transplants and heart-lung transplants seem to be more cost effective than a single lung transplant, but more people benefit from a single lung transplant .The cost effectiveness of a lung transplant is likely to be an ongoing debate, which will probably not reach a conclusion until there are enough lungs for everyone in need of them [3].

1.4 Referral and placement on a lung transplant list

General background

Lung transplantation is a procedure for patients with advanced lung disease without the possibility of receiving another therapy that prolongs life. Since lungs for transplantation are a scarce resource, the referral to a transplant center and being put on the transplant list can be a complicated process. Questions raised before lung transplantation include: (1) what is the indication? (2) what should govern the selection of candidates? (3) what is the fitting surgical approach, and (4) will the outcomes be good enough? [4].

The decision to refer a patient to a center or place the patient on a lung transplant waiting list should be made with the aim of increasing survival as much as possible. A factor in this is surviving the surgery and the subsequent immunosuppressive treatment. The patient must also withstand drug toxicity and rejection [5]. Being referred to a center is not the same as automatically getting on the lung transplant list [6].

1.4.1 Leading indications

The leading indications for lung transplantation are Chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), and alpha-1 antitrypsin deficiency (AATD). COPD is the leading indication for a lung transplant worldwide, with a third of performed lung transplants falling into this indication category. IPF is gaining on COPD, however, and is the leading indication in the USA and worldwide in second place. Less frequent indications are CF (16%), emphysema caused by AATD (7%), sarcoidosis (3%), non-CF bronchiectasis (3%), IPAH (2%), and lymphangioleomyomatosis (1%) [5].

1.4.2 Risk of death and increased survival

The two most important factors in referring and listing patients on a lung transplant list are the risk of death and the increased survival rate. Those two variables make it possible to decide which patients should be referred and then which ones should be placed on the transplant list.

1.4.2.1 IPF

The risk factors of mortality in patients diagnosed with fibrosis include lowering of FVC% values, male gender, and greater age. The best method to diagnose the risk of death while waiting on a transplant list is the six minute walk, which has more prediction strength than the FVC value [7].

1.4.2.2 Bronchiolitis caused by Rheumatoid arthritis

One of the indications for a lung transplant is bronchiolitis caused by Rheumatoid arthritis. The problems these patients face are various but in general they have increased risk of death with older age at the onset of the disease, male gender, and more severe RA. After the development of bronchiolitis, the median survival time is only 2.6 years [8].

1.4.2.3 Cystic fibrosis

A large portion of cystic fibrosis (CF) patients die early on in adulthood. Most die within two years of being on the waiting list for a lung transplant [9]. Surfactant dysfunction [10] and the decline in the natural clearing of bacteria cause increased occurrences of bacterial infections in CF patients with Staphylococcus aureus and pseudomonas aeruginosa. These bacteria are known risk factors for rapid decline in lung function in CF patients [11].

FEV1 is the best predictor of survival, and a 10% decrease in FEV1 between follow up years amounts to double the chance of death. Female gender and young patients also amount to about twice the risk of respiratory failure [9]. Early age of onset, female gender, and a 30% downfall in FEV1% should be considered when referring patients with cystic fibrosis to a lung transplant center, with the idea in mind that females and patients with early onset should maybe be referred earlier [9]. Other causes for referral can be chronic heamoptysis and non-treatable infectious exacerbations.

1.4.2.4 COPD

COPD is a major indication for lung transplantation, and can be defined as a failure in reversing a limitation in air flow. FEV1 has often been used to grade COPD [12]. One method used to measure the risk of death in COPD patients is the BODE index, which takes into account BMI, airway obstruction, exercise capacity, and dyspnoea [12]. The BODE index is a good predictor of death for any reason including lung problems [13]. It is therefore used to evaluate the disease severity of referred COPD patients before possible LTx [14]. The risk factors for death in COPD patients include acute exacerbations, higher age, and arterial carbon dioxide tension. As the frequency of exacerbations increases, so does the risk of death [15].

COPD patients have increased quality of life regardless of their BODE scores before the transplant, but the ones that benefit the most are the ones that are the most severely ill. That means that the BODE score should be used to determine which patient needs the lung the most [12].

1.4.2.5 Re-transplantation

There are other factors in the referral and then listing process for ReTx than in primary LTx. The reasons for this are the treatment and the complications of having already had a lung transplant

surgery [4]. The most common reason for a re-transplant is graft failure, which leads to death or adds to other complications that lead to death [4].

When referring a patient in need of a re-transplant, the risk factors for decreased survival rates are patients on ventilator treatment, patients receiving the transplant earlier than two years after the first one, centers having performed less than five re-transplant (ReTx) operations, and centers who have had less than five patients in need of a ReTx [16]. Since lungs for transplantation are a scarce resource, the guidelines should be strict about ReTx [11]. A collaborative study of Re-Tx in the Nordic countries has recently been published, and shows that survival can be as good as the first LTx if careful selection of appropriate patients is made [17].

Lung transplant surgery is a life changing procedure, but the donor lungs required for transplant surgery are scarce. Therefore, the referral and waitlist processes should be thorough. To make sure that the sickest patients receive a transplant; however, this should be done without taking into account the patients who need a surgery before they get sicker.

1.5 Ex-Vivo Lung Perfusion (EVLP)

EVLP can be a partial solution to one of the troubles facing lung transplantation, namely the shortage of transplantable lungs [18]. The EVLP technique was developed with the aim of lowering the high number (60–80%) of donor lungs that are not suitable for transplantation and therefore rejected [18]. The EVLP technique is based on the perfusion of the donor lungs in an ex vivo circuit using a heart-lung machine, and concomitant ventilation of the graft using a respirator. The aim is to reduce pulmonary edema and improve atelectasis to make the lungs more viable and transplantable [18].

There is an ongoing cohort study in Sweden comparing the survival of patients with EVLP treated lungs to the ones receiving normally transplanted lungs. It's still early in the follow up, but so far the one-year results are promising and up to this point the EVLP lung transplant patients are not faring worse than the patients with normal lungs [19].

1.6 The treatment after lung transplantation

1.6.1 General

After the lung transplant, the patients need regular and consistent follow up. Adherence to the treatment is vital, so the follow up is very strict. The follow up consists of regular use of medications, modified diet, regular clinical checkups, and the patient can neither smoke nor drink alcohol [20]. They should also be careful about sun exposure due to an increased risk of skin cancer.

Adherence to the medications is a problem because it affects the daily life of a patient greatly; a lung transplant patient receives on average 10 drugs per day [20].

The medications that the patients receive are usually a mixture of immunosuppressive drugs, prophylactic treatment against infections, drugs against side effects, treatment against associated pathologies, and other drugs [20].

1.6.2 Immunosuppressive treatment

The immunosuppressive treatment to reduce the occurrence of rejection is usually a triple drug therapy: the calcineurin inhibitors cyclosporine or tacrolimus, the antiproliferative agent azathioprine or mycophenolate, and corticosteroids. Also, 50% of centers utilize induction therapy for immunosuppression, polyclonal antibody preparations, interleukin 2 receptor antagonists, or alemtuzumab [21].

1.6.2.1 Prophylaxis

Prophylactic treatment against infections starts with preventive measures by the patient and then three types of prophylactic treatment: vaccination, general prophylaxis therapy, and pre-emptive therapy [22].

1.6.2.2 Vaccination

The vaccination treatment is usually pneumococcal or the yearly vaccination for influenza [22].

1.6.2.3 General prophylaxis

The general prophylaxis therapy is aimed at four different microbial agents: antibacterial, pneumocystis jirovecci pneumonia (PCP), cytomegalovirus CMV, and antifungal medicine [22]. Broad spectrum antibiotic therapy is a routine treatment for lung transplant patients and is aimed at gram negative microbes [22]. Sulfamethoxazole and trimethoprim are the two parts of PCP prophylaxis which is very successful [23].

CMV prophylaxis is a very important treatment because of its correlation with bronchiolitis obliterans syndrome (BOS), which is the leading cause of graft failure in lung transplant patients after the first year. In 2005, the CMV Expert Advisory Committee recommended prophylactic treatment using valganciclovir for at least 100 days after the transplant [24]. The prophylactic treatment period with valganciclovir in Sweden is three months if both the donor and the recipient are CMV seropositive, but if there is a mismatch—meaning that the recipient is CMV seronegative and the donor is CMV seropositive—then the prophylactic treatment period with valganciclovir used to be six months at the time of this study but today it's 12 months; the treatment should be the same in Iceland.

In one study of how antifungal prophylaxis differs from one center to another, the results were that the majority of centers, 69%, had a universal antifungal prophylaxis in the postoperative period and 31% had a pre-emptive approach to airway colonization of fungi. The most common drugs used for antifungal prophylaxis were either only amphotericin B deoxicholate or the amphotericin in a combination with itroconazole [23].

1.7 Primary graft dysfunction (PGD)

PGD affects 10–25% of all lung transplant patients and is a severe form of ischemia/reperfusion acute lung injury to the lung graft [25]. After the lung transplant, PGD is heavily connected to increased mortality and morbidity. The likelihood of death in the first 30 days is eight times greater for patients who suffer from PGD. Of those who survive the first year, there is an increase in the occurrence of BOS in these patients and in worse long-term lung function [25].

The International Society for Heart and Lung Transplantation (ISHLT) has proposed a definition of PGD, defining it according to Pa_{02}/Fi_{O2} and chest infiltrates measured by radiologic evidence on specific times leading up to 72 hours. This makes it easier to compare the results of different studies to understand better the risk that PGD poses for lung transplant recipients. That is important because PGD is one of the risk factors of developing BOS risks in lung transplant patient [25].

1.8 The complications of the treatment of lung transplant patients

The complications following the lung transplant, which are not connected to pulmonary function, are hematologic complication, osteoporosis, renal failure, diabetes, avascular necrosis, malignancy, cardiovascular complications, gastrointestinal complications, and thromboembolic disease.

1.8.1 Hematologic complications

Azathioprine, mycophenolate mofetil, Cytoxan, and prophylactic and antiinfectious medication like valganciclovir all contribute to cytopenia, the most common hematologic complication in lung transplant patients [26]. The renal failure in some lung transplant patients contributes to anemia; the iron deficiency and low erythropoietin levels are treated with iron supplementation and erythropoietin, which has been shown to improve hemoglobin levels [27]

1.8.2 Osteoporosis

Osteoporosis is one of the complications that affects the daily lives of the lung transplant patients the most. There are about 6–18% of patients that have bone fractures in the first year and the BMD reduced by 4–12% .The bone loss because of osteoporosis seems to be accelerated for all solid organ transplants in the first three to six months [26]. The osteoporosis is thought to be caused by corticosteroids and other immunosuppressive medications [28]. There have been a lot of attempts to solve the problem of osteoporosis in lung transplant patients but supplements like vitamin D and calcium have not been shown to prevent the development of osteoporosis [29]. Calcitriol has been shown to be effective against the bone loss in the first year [30].

1.8.3 Renal failure

One of the most common long term complications for lung transplants is renal dysfunction, since one out of four lung transplant patients has renal dysfunction after the first year and after five years the incidence has increased to 37.8% [26]. Almost all lung transplant patients have a decline in kidney function in six months after the surgery [31]. The renal function matters greatly in these patients, since chronic renal failure makes death four times more likely [32]. Calcineurin inhibitors like cyclosporine and tacrolimus are the most common cause of renal failure since they cause nephrotoxicity, but tacrolimus has been shown to cause less renal dysfunction than cyclosporine [31].

1.8.4 Diabetes

The closest thing to the incidence of renal dysfunction is diabetes affecting one out of every four in the first year and 33.5 % after five years [26]. Having diabetes prior to the transplant increases the

relative odds of death after the transplant. The medications that put patients at an increased risk of developing diabetes are glucocorticoid steroids and calcineurin inhibitors, tacrolimus being worse than cyclosporine in this perspective [33]. It's not just the medicine, as other factors must also be considered. These include older age, obesity, and frequent acute rejection episodes that are treated with high dose steroids [34]. Even though having diabetes prior to the lung transplant results in decreased survival rates, getting diabetes after the transplant has not been correlated to worse survival rates, as in other solid organ transplantation. However, this could be due to there being less time for diabetes to do its damage, since lung transplant patient long term survival is limited [26].

1.8.5 Neurologic complications

Twenty-six percent of lung transplant patients, according to one study, have neurologic complications such as severe headaches, seizures, strokes, and confusion. This was mostly attributed to calcineurin inhibitor toxicity or infections [35]. The treatment to correct the neurologic complications is usually simply substituting either cyclosporine or tacrolimus [26].

1.8.6 Avascular necrosis

Eleven to 22% of solid organ transplant recipients have avascular necrosis in the head of the femoral bone, and being younger than 40 years old is a risk factor [36]. The cause of the avascular necrosis is thought to be high-dose steroids [37]

1.8.7 Malignancy

Malignancies in lung transplant patients tend to occur more often than in other recipients of solid organs, but in general solid organ recipients are more prone to malignancy than the general public [26]. The increased possibility of malignancy in solid organ recipients can be up to three to four times that of the general public and the incidence of specific cancer can be 100 times more than in the general public [38]. In lung transplant patients, the prevalence of malignancies is 3.7% in the first year, 12.4% five years from the transplant, and one out of four in the 10 years after the transplant [26]. Skin cancer and post-transplant lymphoproliferative disease (PTLD) are the most common of the malignancies affecting the lung transplant patient [26]. The difference in the timing of skin cancer and PTLD is that PTLD is the most common cancer in the first two years and skin cancer is the most common malignancy after that [26]. PTLD is caused by abnormal lymphoid proliferation and has an incidence of 0.8% to up to 20% [39] . PTLD is related to the reactivation of EBV and the majority of cases involve B cells, but 14% involve T cells [26]. The major risk factors for developing PTLD are a seronegative EBV status of the recipient and the intensity of immunosuppression [26]. Lowering immunosuppression is the main aim of treatment against PTLD, but rituximab has also been shown to be successful [40]

1.8.8 Cardiovascular complications

Cardiovascular complications in lung transplant recipients are mainly because of the immunosuppressive therapy, which has a part in causing diabetes, hypertension, hyperlipidemia and renal disease, as previously mentioned. Of the cardiovascular complications in a lung transplant

patient, hypertension is the most common, with half of the patients having hypertension after the first year and 85.6% after five years. Second to hypertension is hyperlipidemia, with one fifth of the lung transplant patients suffering from this disease in the first year and half of the patients after five years [26]. Hyperlipidemia is treated with statins which can improve survival in lung transplant patients [41]. Even though a large portion of lung transplant patients suffer from cardiovascular complications, they account for only 5.3% of deaths in patients who survive the first year [26]..

1.8.9 Gastrointestinal complications

There can be life threatening gastrointestinal problems in the early part of the postoperative period, such as ileus and colonic perforations [26]. Gastrointestinal problems are common for lung transplant patients—up to 50% are estimated to have one or more gastrointestinal complaints [13], this is probably because of the high dose of immunosuppressive drugs [26]. Long term complaints of LTR are nausea (the most common), abdominal pain, gastro esophageal, diarrhea, reflux disease, constipation, and vomiting [42]. Nausea is most likely a result of the treatment with calcineurin inhibitors and valganciclovir [42]. Even though gastrointestinal problems can by mild, they can affect the life of the LTR greatly [42].

1.8.10 Thromboembolic disease

Venous thromboembolism has an incidence of 8.6% to 29% in lung transplant patients. The mean time from the surgery to a venous thromboembolism event is according to two studies 47 days to 69 days [26].

1.9 Mechanical ventilation vs. extracorporeal lung support technologies

Mechanical ventilation is a life saving method that has for decades been the first choice treatment for respiratory failure [43]. However, even though mechanical ventilation is a life saving method, patients can suffer from severe hypoxia and hypercapnea. The injury sustained from the mechanical part can have adverse affect on the lungs and the survival of the patients [43]. So that's why experiments with changing the mechanical ventilation have been developed. The experiments include reducing the pressure and the volume of gas delivered [43]. Because of the insufficiency of mechanical ventilation, extracorporeal lung support technologies can help with the hypoxia and the hypercapnea in patients with lung failure by making the oxygen and carbon dioxide transfer easier. It can also give the lungs a rest to heal [43]. The extracorporeal lung support technologies are focused on taking the blood out of the body to change the oxygen or the CO_2 concentration. One method is using an oxygenator to exchange oxygen and CO_2; the other is to take CO_2 out of the blood [43].

1.10 Bronchiolitis obliterans syndrome (BOS)

1.10.1 General background

Bronchiolitis obliterans syndrome (BOS) is an irreversible chronic rejection of the lung graft after LTR. BOS is defined as reduced FEV1 values over time in comparison to a reference basal value

established from the best spirometric values during the first postoperative year. The reduction in FEV1 values is caused by scarring and fibro proliferative changes in the small airways of the graft [44].

1.10.2 BO vs. BOS

The chronic rejection of the lung graft used to be defined as BO. BO is a fibrotic change in a non-cartilaginous airway in a lung graft. But the sensitivity of a transbronchial biopsy to determine BO is only 28%, since the changes occur only patchy in the lung. The insufficient sensitivity led to a revision of the diagnosis of chronic rejection, which led to the development of the concept BOS [44].

1.10.3 Diagnosing BOS

BOS is defined according to the average of two best FEV1 values during the first year, so the average of the best two values is considered as a 100% reference value so physicians can track regression of the function of the lung graft [44]. To diagnose BOS requires a sustained pulmonary decline with a reduced FEV1 for more than three weeks [44]. Other spirometric values have been investigated, and it appears that reduction in midspirometric $FEV1_{25-75}$ can be used as an early indicator of BOS [44].

Table 1 Classification of bronchiolitis obliterans syndrome

0 FEV1 > 90% of baseline & FEF_{25-75} > 75% of baseline
0-p FEV1 81-90% of baseline &/or FEF_{25-75} ≤ 75% of baseline
1 FEV1 66-80% of baseline
2 FEV1 51-65% of baseline
3 FEV1 ≤ 50% of baseline

In table 1 the classification of BOS is explained according to FEV1 and FEF_{25-75}. a) 0-p is an early indication of potential BOS [44].

1.10.4 Accelerated progression of BOS

The clinical progression of BOS is that it gets worse over time. In the international lung transplantation register, freedom from BOS in the first, third, and the fifth postoperative years is shown to be 82%, 42%, and 25%, respectively [45]. Clinical factors linked to an accelerated progression of BOS are female LTR, IPF, early onset of BOS, and receiving a single lung transplant. [46]. Also, early onset of BOS is linked to number of acute rejections [47].

1.10.5 Risk factors for BOS

To be able to prevent or treat BOS requires an increased understanding of the causes of BOS. Some of the risk factors are acute rejection [48]; airway colonization of GP and GN bacteria and fungi [49], especially Aspergillus [50]; SLTx in COPD patients [51]; community acquired viral infections [52]; CMV infection [53] and EBV reactivation [54]; Primary graft dysfunction [55]; gastro-esophageal reflux [56]; HLA DR and HLA B mismatches [57]; and Collagen V antigen [58].

1.10.6 Treatment to prevent and slow the progress of BOS

The treatment to prevent and manage BOS is ongoing and there has been some research to explore different immunosuppressive regimens in this aspect [59]. Tacrolimus has in one study shown to stabilize spirometric values during the first year, compared to cyclosporine [59]. Tacrolimus has also been shown to lower the rate of acute rejection, which leads to less progression to BOS. Mycophenolate mofetil has been effective against progression of BOS after its been diagnosed [60]. Azitromycin, a macrolide, has shown to be effective in slowing BOS progression [61].

1.10.7 Treatment to cure BOS

The only treatment for BOS today is a re-transplantation, which is controversial because transplantable lungs are a scarce resource. The biggest argument against re-transplantation is that the survival rates are not as high as for patients having their first transplantation. However, progress is being made, and re-transplanted patients are surviving for a longer time in recent studies [62].

Considering the aforementioned evidence, coupled with the fact that BOS is the leading cause of death after the first year [63], the treatment to prevent BOS with immunosuppressant is essential to long-term survival. Ongoing research into the exact pathology of this syndrome will lead to new therapeutic options, which will hopefully lead to growing survival rates.

1.11 RAS

RAS is a type of chronic rejection that usually presents itself with infiltrates on a CT scan. RAS, like BOS, is a decline of lung function in a lung transplant recipient, but is different from BOS as in RAS the decline in FEV1 is not obstructive but restrictive. Being restrictive is defined as a 10% decline of the postoperative TLC baseline [64].

1.12 Work

A study of lung transplant patients in Germany showed that working after the transplant doesn't seem to have an effect on survival but increases quality of life. The factors that seem to affect the decision of a lung transplant patient to go back to work are education and physical fitness, and 38% of the patients went back to work, which is similar to the rates in other countries [65].

2 Objective

Lung transplantation has become a valid treatment for end stage lung disease, with more reported surgeries every year in the world. There was an increase in lung transplantation of Icelandic patients in 2010 to 2012, almost half of all Icelanders who have ever received a lung transplant. This increase in the number of patients made it interesting to compare how the Icelanders were faring compared to the Swedish patients receiving lung transplants at the same center and during the same time period.

The two groups were compared according to the state of the lung graft by comparing the development of chronic rejection, CMV treatment to look at one of the most important aspects of keeping the lung allograft BOS free, and how many times the patients needed treatment for raised values of CMV. Lung function values and plasma clearance were also compared.

3 Methods

3.1 Study design

The patients in this study had a lung transplantation performed in the years 2010 to 2012 at the Sahlgrenska University Hospital Gothenburg. Altogether at Sahlgrenska in that time frame there were 121 surgeries performed on 120 patients, and ten of these surgeries were done on nine Icelandic patients. To compare how the two patient groups fared after the transplantation, they were compared according to their lung function values, BOS status, plasma clearance, CMV status, treatment for CMV infection and number of treatments for raised levels of CMV, and survival and occupation status.

3.2 Approval

Before the project started, we obtained a permit from Ólafur Baldursson, the chief executive of medicine at the University Hospital of Iceland Landspitalinn and from The National Bioethics Committee Science ethics committee (**15-005-afg**).

3.3 Patients

The patients that we gathered information on had undergone a lung transplantion at Sahlgrenska University Hospital in Gothenburg over three years from 2010–2012. The objective of the study was to compare the Icelandic lung transplant recipients to the Swedish lung transplant recipients to see if one group was doing better than the other after lung transplantation, or if their clinical development differed.

3.4 Collecting data

Data was collected in Iceland and Sweden. In Iceland the information about lung function and kidney function was collected from the test result system Heilsugátt. General Information and information about the CMV status, CMV treatment, and the number of Valcyte treatments per patient was collected from the patient file system Saga, and the information about occupation was collected from the transplant coordinator. In Sweden, all information was collected from the patient file system except the information about occupation, which was collected from a nurse that oversees the Swedish lung transplant recipients. The information collected was stored in Microsoft Excel files.

3.5 Calculating significance

The independent samples T test in the statistical software SPSS was used to calculate any statistical differences between the two groups compared.

3.6 Kidney function

3.6.1 Plasma clearance

Plasma clearance is the overall capability of the human body to eliminate a drug.

3.6.2 Calculating plasma clearance

3.6.2.1 Different methods

There are different methods used in Iceland and Sweden to measure plasma clearance; in Sweden, they use ^{51}Cr-EDTA clearance, which is a very sensitive measurement of plasma clearance, while in Iceland we use creatinine clearance to calculate plasma clearance by using the MDRD formula.

3.6.2.2 MDRD equation

GFR (mL/min/1.73 m2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American).

3.6.2.3 Problems with using creatinine and the MDRD equation

The sensitivity of the MDRD equation with plasma clearance values above 60 ml/min is insufficient. This is why plasma clearance values obtained using the MDRD equation over 60ml/min are written as above 60ml/min, not the actual value.

3.6.2.4 Comparing plasma clearance

To be able to compare the plasma clearance levels of the two groups, the values above 60 ml/min had to be calculated again for the Icelandic patients using the MDRD equation, because they were listed as above 60 ml/min in the Heilsugátt system.

3.7 Lung function

3.7.1 Spirometry

Spirometry is a device used to measure lung function values such as FEV1 and FVC. The patient blows into the device and the device measures the air flow. The FEV1 value is the air flow measured in the first second, and the FVC value is the total air flow measured. Baseline is the average of the two best FEV1 values in the first year after the transplantation. FEF_{25-75} is the value of the air flow measured by the spirometry in the middle of expiration. The FEV1 value is the air flow measured in the first second by spirometry. The FEV1% value is the FEV1 value obtained by the spirometry divided by the FEV1 reference value.

The corrected FEV1% value is the same as the FEV1% but corrected because of the difference of the reference values in Iceland and Sweden, Iceland using the American system and Sweden using the European system. The FVC value is the total air flow measured by spirometry. The FVC% value is the FVC value obtained by spirometry divided by the FVC reference value. The corrected FVC% is the same as the FVC%, but corrected for the difference of reference values in Iceland and Sweden, Iceland using the American system and Sweden using the European system. Reference values are lung function values of the general population used to calculate FEV1% and FVC%. The reference values are obtained by making spirometric tests on healthy people; they are defined according to sex, age, height.

The Hanskinson equation from 1999 was used to calculate the Swedish FEV1% and FVC% values again according to the American reference system.

3.8 Chronic rejection

3.8.1 BOS

BOS is the manifestation of a chronic rejection in a LTR, defined by spirometric values.

3.8.2 RAS

RAS is a very serious chronic rejection defined by radiographic evidence of fibrotic infiltrations and a restrictive lung function.

3.9 CMV

3.9.1 CMV status

CMV status refers to the CMV serum status of a patient and is measured by detecting IgG antibodies for CMV. The CMV status of the lung donor and the lung recipient are used to evaluate how long the prophylactic treatment period with Valcyte should be. There are general guidelines that recommend that lung transplant recipients should receive Valcyte treatment for the first 100 days after the transplant. This treatment is important because raised levels of CMV are one of the most important risk factors for BOS. A mismatched patient is a patient that has the CMV status D+/R-.

Table 2 shows how the CMV prophylaxis for lung transplant recipients after the lung transplants in 2010 and 2012 in Iceland and Sweden should have been.

Table 2 CMV prophylaxis

CMV status(donor/recipient)	Sweden/Iceland
(D+/R+)	3/3
(D-/R+)	3/3
(D-/R-)	0/0
(D+/R-)	[a]6/6

Table 2 shows according to CMV status the CMV prophylaxis for Icelandic and Swedish lung transplant recipients that received lung transplant surgery in the years 2010-2012. a) today the treatment is 12 months.

3.9.2 CMV treatment after prophylaxis

If the patients are measured with raised levels of CMV after prophylactic therapy, then they are treated with Valcyte in both countries.

3.10 The matching process

Twenty Swedish patients were matched to the 10 Icelandic patients, according to clinical reason for the lung transplant, sex, age, and number of lungs received.

The Swedish lung transplant patients who were excluded from the matching process were the ones that; survived for less than 6 months, did not comply to treatment and the ones who had diseases that were not comparable: CF, PAH, Eisenmenger, Sarcoidosis, LAM, Histiocytosis X, CPFE, GVH, SLE, and Kartageners syndrome.

Table 3 The matching process

Exclusion criteria	Number. of patients
Died within 6 months	9
Disease not comparable	29
AATD	
Women	9
Men DL	1
Men Age	1
AATD total	11
BOS	
Age	3
1. COPD	
2. Bronchiectasis	
SL	10
Age	3
Non compliant to treatment	1
COPD total	14
LF	
Women	14
Men DL	9
Men Age	2
LF total	25
RA, bronchiolitis	
Total nr. of patients:	121
Patients excluded:	91
Patients in the study:	30

Table 3 shows how well the matching process went. a) The Swedish RA bronchiolitis patients were matched to the Icelandic bronchiolitis patient, but there were only two RA bronchiolitis patients so no RA bronchiolitis patient was excluded. b) 1. COPD, 2. Bronchiectasis: The Swedish COPD patients were first matched to the Icelandic COPD patients, then the rest of the COPD patients were matched to the Icelandic bronchiectasis patients.

3.10.1 Problems with the matching process

3.10.1.1 Bronchiolitis

The additional matching of the number of lungs received was possible for all the clinical reasons for receiving a transplant except for the RA-bronchiolitis. This was because there were only two patients with bronchiolitis as a clinical reason for the transplant and it wasn't ethical to pick a patient with a

different clinical reason for the transplant instead of the RA bronchiolitis who didn't receive the same number of lungs as the Icelander. The patient was included in the study but not the patient's lung function values.

3.10.1.2 Bronchiectasis

The only Swedish patient with bronchiectasis as the main reason for the surgery died within 6 months of the surgery. Swedish COPD patients were used for comparison to the Icelandic bronchiectasis patients.

4 Results

4.1 Patient groups

4.1.1 General information

In Table 4 one can see that the age is fairly close, Sweden's patients being about four years older on average. The sex is not equal, with women being in the majority of Sweden's patients and men being in the majority in the Icelandic group. Most Icelanders had a transplant in 2012, but Sweden's numbers are constant.

For most indications, there are the same ratios in both patient groups, except for COPD and bronchiectasis.. There are about the same number of SL and DL in both groups, with one Swedish patient with the wrong number of lungs. There were equal numbers of the types of lung received by the lung transplant patients. There is a small minority still working, but the majority has stopped working and is either out of work like the majority of the Icelandic patients or retired like the majority of the Swedish group. Fifteen percent of Sweden's patients have died and none in the Icelandic group but 10% of Iceland's patients have had a re-transplant due to graft failure.

Table 4 General information

General information		Iceland	Sweden
Patient sample	number of patients	10	20
		Years	
Age	Average age	52.3	56.0
		(%)	
Sex	Male	60	40
	Female	40	60
Indication for LTx	AATD	10	10
	BOS	10	10
	Lung fibrosis	10	10
	COPD	40	60
	bronchiolitis obliterans	10	10
	Bronchiectasis	20	0
Nr. of lungs received	SL	20	25
	DL	80	75
Type of donor lung	Regular	90	90
	EPLV lungs	10	10
Year of the transplant	2010	20	30
	2011	30	35
	2012	50	35
Survival	Alive	100	85
	Dead	0	15
Occupation	Working	20	15
	Not working	70	35
	Early retirement	0	25
	Retirement	0	10
	Died	0	15
	ReTx	10	0

Table 4 shows the comparison of Iceland and Sweden's lung transplant recipients in the years 2010–2012 according to the number of patients in the study, age, sex, indication for the lung transplant, number of lungs received, type of donor lung, year of the transplant, survival, and occupation.

4.2 Chronic rejection

Shown in Table 5 is the ratio of the two groups, comparing the groups for chronic rejection. Iceland is doing a little worse than Sweden, with a higher ratio of early BOS, BOS, and the only patient with RAS is in the Icelandic group. Half of the Swedish patients are BOS free compared to 30% of the Icelandic group also there is a difference between the two countries in the time until BOS with Sweden doing a little better with a little longer time until the development of chronic rejection.

Table 5 Chronic rejection among Iceland's and Sweden's lung transplant recipient

Chronic rejection	Iceland	Sweden
	%	
Early BOS	10	5
BOS	50	45
RAS	10	0
Not BOS	30	50
	Years	
Time until BOS/developing BOS	2.1	2.2

Table 5 shows the comparison of Iceland and Sweden's lung transplant recipients in the years 2010–2012, according to the status of chronic rejection in the donor lung.

4.3 CMV treatment

As one can see from Table 6, the ratios are fairly similar, with 15% of Sweden's group mismatched (D+ / R-) compared to Iceland's 10%. And 90% of the Icelanders with either D+ / R+ or D- / R+ receive the same treatment compared to Swedens 85%. There are more treated for raised levels of CMV and more numbers of treatment in the icelandic group than in the Swedish group and the only mismatch patient in the Icelandic group is treated more often than the Swedish mismatched patients.

Table 6 CMV in Iceland's and Sweden's lung transplant recipients.

CMV		Iceland	Sweden
		%	
	D+ / R-	10	15
	D+ / R+	80	55
Status	D- / R+	10	30
	Treated	60	35
Treated	Not treated	40	65
	1	10	30
	2	40	0
	3	0	10
Nr. of treatments	>3	10	0
		nr of treatments	
Mismatch		7	1

Table 6 shows the comparison of Iceland and Sweden's lung transplant recipients in the years 2010–2012, according to the ratio of CMV status, treatments for CMV and how many were treated, and how many treatments the mismatched patients in each group received.

4.4 Lung function values

Figure 1 and Figure 2 both show that the two groups have a substantial increase in FEV1 and FVC from before the surgery until the first follow up year, but Sweden gains more than Iceland and has higher levels in follow up years two and three, yet is similar to Iceland in the fourth year.

The change in FEV1 and FVC on display in Figure 5 and Figure 6 shows the difference between the two groups mentioned above, that Sweden gains a lot more after the surgery but there isn't a big difference between the two groups in change after the first year of follow up.

In FEV1% and FVC% values, which are on display in Figure 3 and Figure 4, show that Iceland and Sweden have a great rise in FEV1% and FVC% after the transplant but Sweden gains more in FEV1% and FVC% than Iceland in the first year of follow up. It is also shown that Sweden keeps having higher FEV1% and FVC% values throughout the follow up years; the difference in the first and the second years is close to being significant, as displayed in Table 7 and Table 8

The change in FEV1% and FVC% on display in Figure 7 and Figure 8 is the same as has been mentioned above—that there is a great increase from before the surgery until the first year but the difference in the change in FEV1% and FVC% is small after the first year of follow up. The difference in the change from before to the first year of follow up is significant, as shown in Table 9 and Table 10.

After seeing the difference in FEV1% and FVC% there were two ideas about what could be causing this : (1) the difference in reference values and (2) that Sweden's COPD patients were receiving bigger lungs that Iceland's COPD patients. The corrected version is on display in Figure 3 and Figure 4 and there is still a difference between the two groups So we looked into other options and the idea was that COPD patients could be giving Sweden better values as the expansion in the

thoracic cage could be the factor, so these patients could receive bigger lungs that their reference values give indication to.

As displayed in Figure 9 and Figure 10, Sweden's COPD patients have a great increase in FEV1% and FVC% compared to before the surgery and keep increasing on average compared to Iceland's COPD group, which rises in the beginning but falls after the second year and is in general lower in FEV1% and FVC% than Sweden's COPD patients.

Comparing Sweden's COPD and Iceland's non-COPD patients, displayed in Figure 11 and Figure 12, there is a greater increase in Sweden's COPD group and they stay above Iceland's non-COPD throughout the follow up years. The difference in the second year is borderline significant (Table 11 and Table 12).

Figure 1 Follow up of FEV1

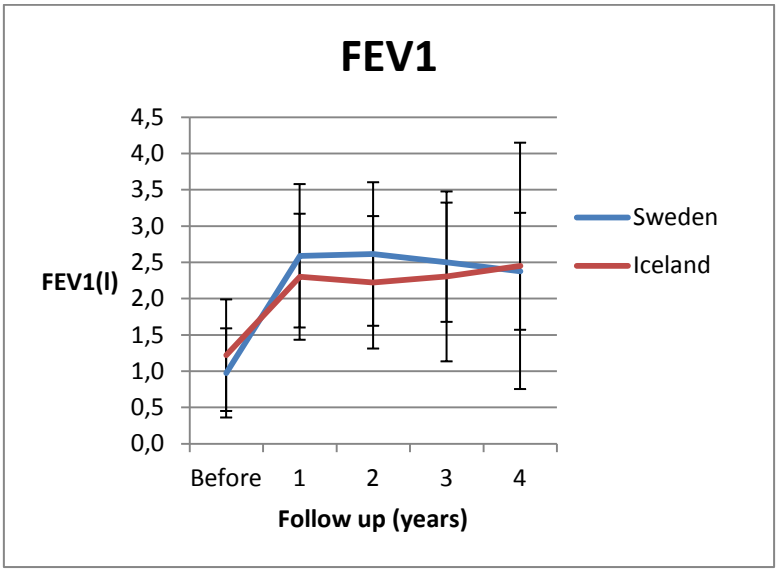

Figure 1 shows four years of follow up of FEV1 values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Figure 2 Follow up of FVC

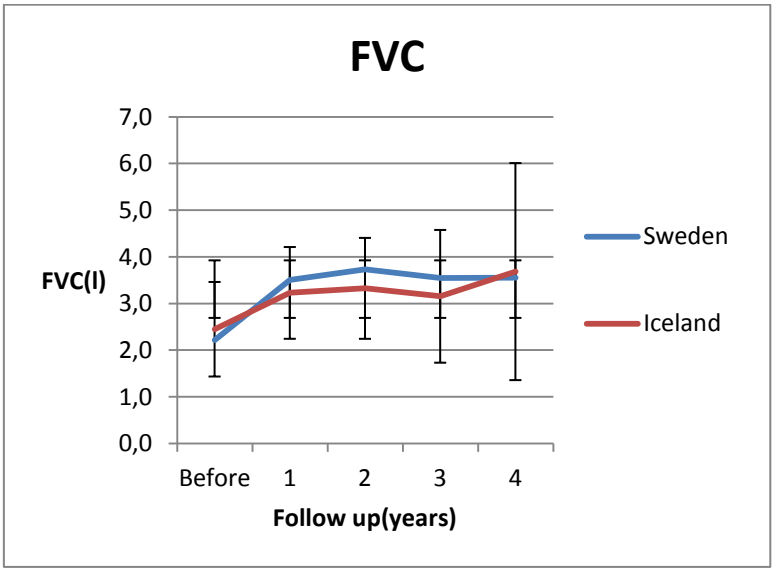

Figure 2 shows four years of follow up of FVC values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Figure 3 Follow up of FEV1% with the recalculated FEV1% values for Sweden

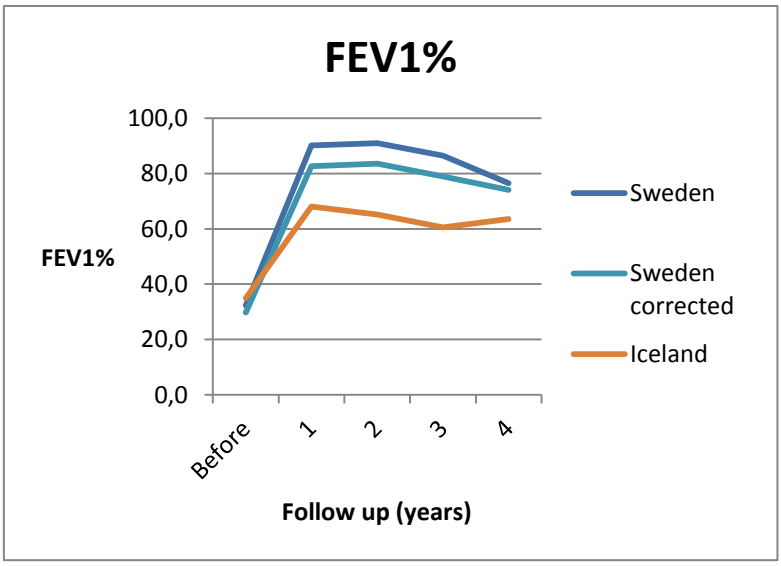

Figure 3 shows four years of follow up of FEV1% values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012. It shows both the FEV1% values obtained in Sweden and the re-calculated FEV1% values of Sweden according to the American system.

Table 7 Significance of follow up of FEV1%

Follow up	Group	N	Mean	Std. Deviation	Sig.
First year	Sweden	18	90.1	33.4	.078
	Iceland	10	68.0	24.3	
Second year	Sweden	15	90.9	35.4	.070
	Iceland	9	65.1	25.5	

Table 7 shows the significance of the comparison of four years of follow up of FEV1% values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012. a) This is the significance of comparison to Sweden's FEV1% values before they were calculated using the American system.

Figure 4 Follow up of FVC% with the recalculated FVC% values for Sweden

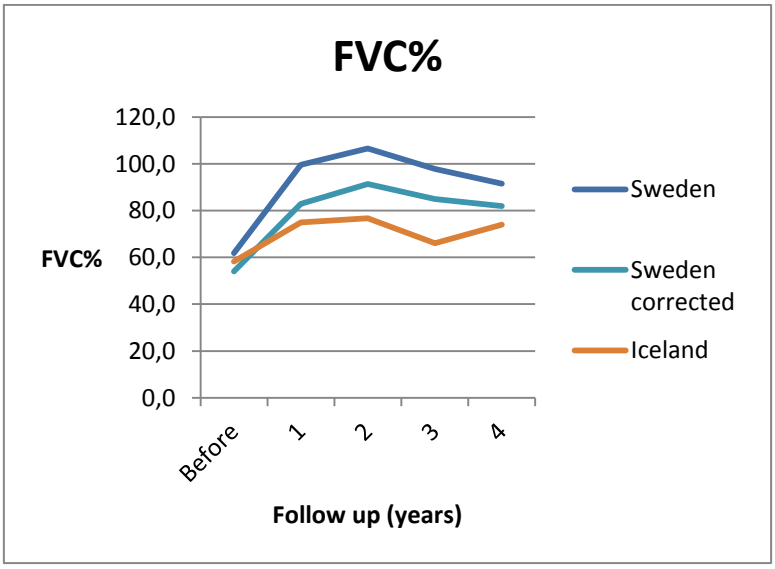

Figure 4 shows four years of follow up of FVC% values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012. a) It shows both the FVC% values obtained in Sweden and the re-calculated FVC% values of Sweden according to the American system.

Table 8 Significance of follow up of FVC%

Follow up	Group	N	Mean	Std. Deviation	Sig.
Firstyear	Sweden	18	99.6	30.3	.031
	Iceland	10	75.0	20.5	
Secondyear	Sweden	14	106.6	30.5	.020
	Iceland	9	76.7	22.6	
Thirdyear	Sweden	9	97.8	26.1	.072
	Iceland	4	66.0	27.7	

Table 8 shows the significance of the comparison of four years of follow up of FVC% values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012 a)

This is the significance of comparison to Sweden's FVC% values before they were calculated using the American system.

Figure 5 Follow up of the change in FEV1

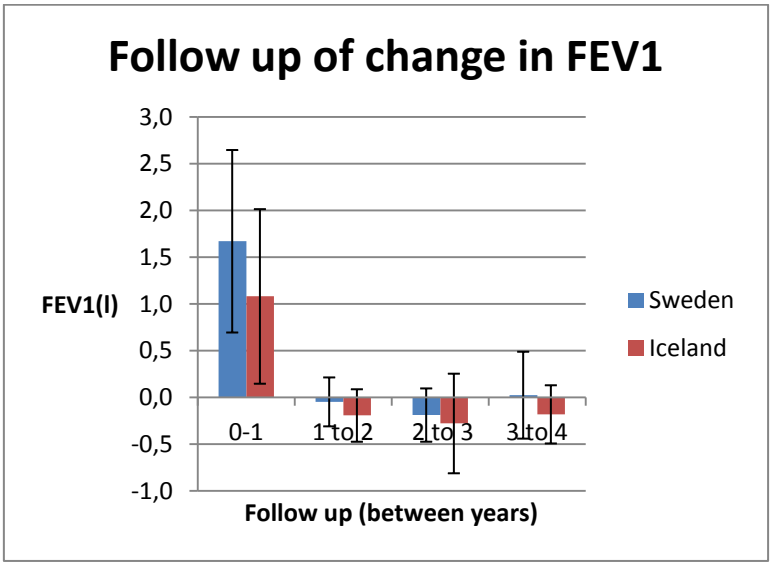

Figure 5 shows four years of follow up of the change in FEV1 values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Figure 6 Follow up of the change in FVC

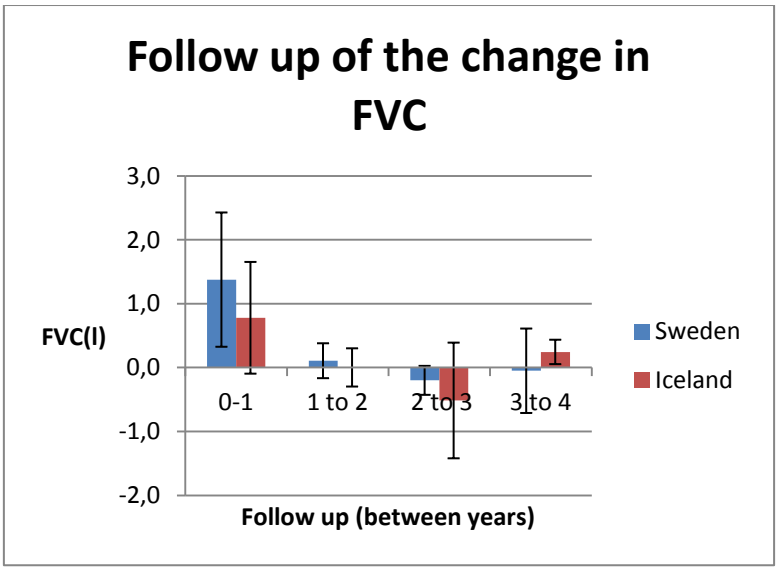

Figure 6 shows four years of follow up of the change in FVC values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Figure 7 Follow up of the change in FEV1%

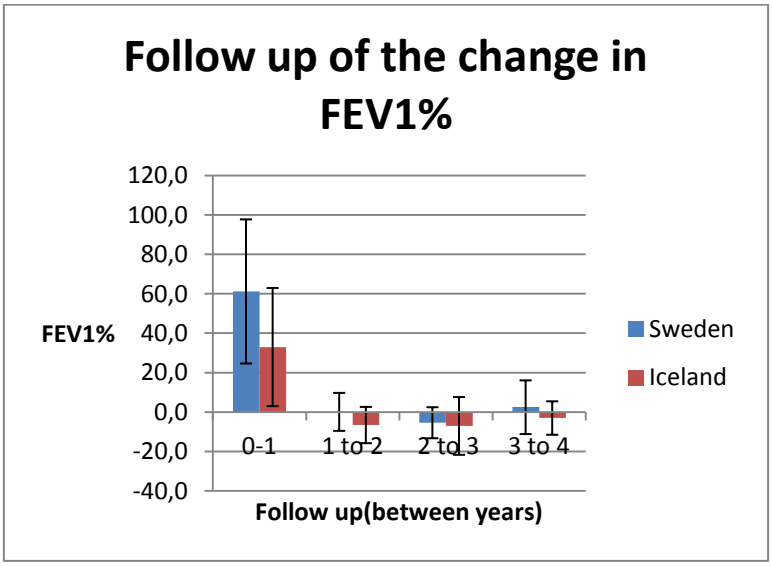

Figure 7 shows four years of follow up of the change in FEV1% values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Table 9 Significance of the follow up of the change in FEV1%

Follow up	Group	N	Mean	Std. Deviation	Sig.
(0-1)	Sweden	18	61.2	36.6	.048
	Iceland	10	33.0	30.0	

Table 9 shows the significance of the comparison of four years of follow up of the change in FEV1% values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Figure 8 Follow up of the change in FVC%

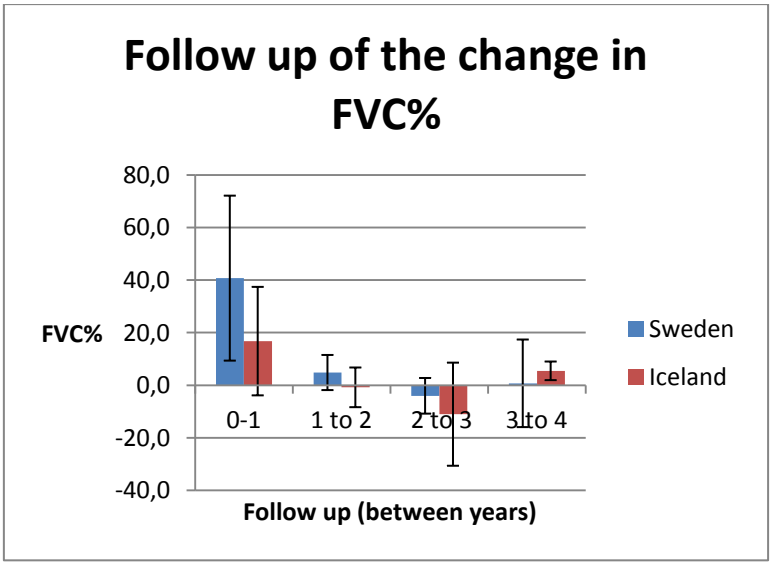

Figure 8 shows four years of follow up of the change in FVC% values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Table 10 Significance of the follow up of the change in FVC%

Follow up	Group	N	Mean	Std. Deviation	Sig.
(0-1)	Sweden	17	40.8	31.4	.042
	Iceland	10	16.8	20.6	
(1-2)	Sweden	14	4.9	6.7	.074
	Iceland	9	-0.8	7.5	

Table 10 shows the significance of the comparison of four years of follow up of the change in FVC% values of Iceland's and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Figure 9 Follow up of FEV1% of COPD/COPD

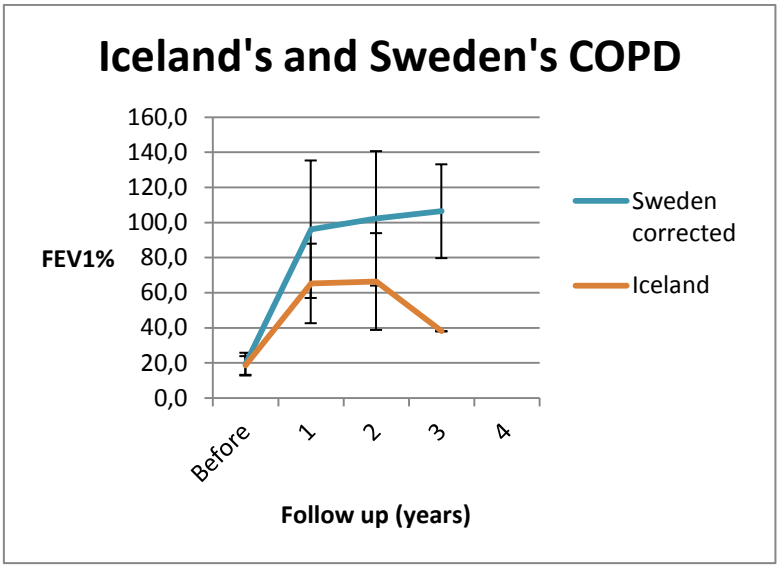

Figure 9 shows four years of follow up of FEV1% values of Iceland and Sweden's COPD lung transplant recipients that received a lung transplant in the years 2010–2012. a) This is Sweden's FEV1% values after they were calculated using the American system.

Figure 10 Follow up of FVC% of COPD/COPD

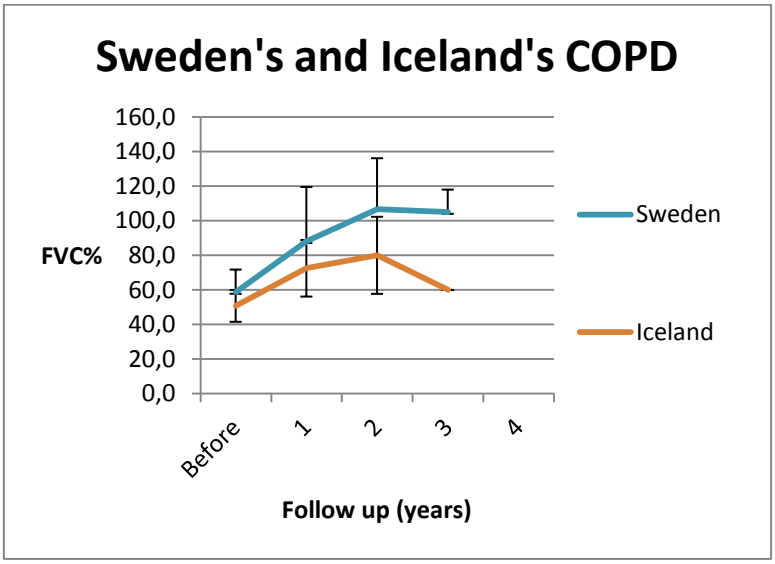

Figure 10 shows four years of follow up of FVC% values of Iceland and Sweden's COPD lung transplant recipients that received a lung transplant in the years 2010–2012. a) This is the significance of comparison to Sweden's FVC% values after they were calculated using the American system.

Figure 11 Follow up of FEV1% of COPD/non-COPD

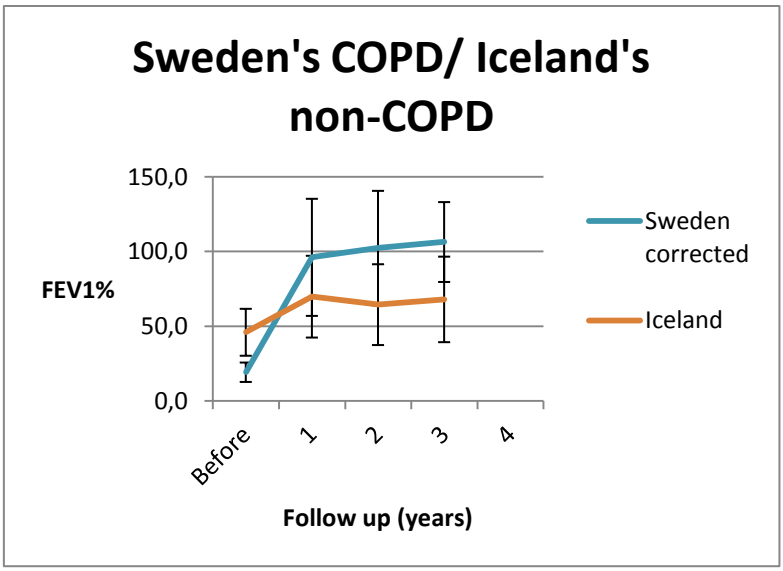

Figure 11 shows four years of follow up of FEV1% values of Iceland's non-COPD and Sweden's COPD lung transplant recipients that received a lung transplant in the years 2010–2012. a) This is Sweden's FEV1% values after they were calculated using the American system.

Table 11 Significance of the follow up of FEV1% COPD/non-COPD

Follow up	Group	N	Mean	Std. Deviation	Sig.
Secondyear	Sweden	6	102.3	38.3	.076
	Iceland	6	64.5	27.0	

Table 11 shows the significance of four years of follow up of the comparison of the FEV1% values of Iceland's non-COPD and Sweden's COPD lung transplant recipients that received a lung transplant in the years 2010–2012 a) This is the significance of comparison to Sweden's FEV1% values after they were calculated using the American system.

Figure 12 Follow up of FVC% of COPD/non-COPD

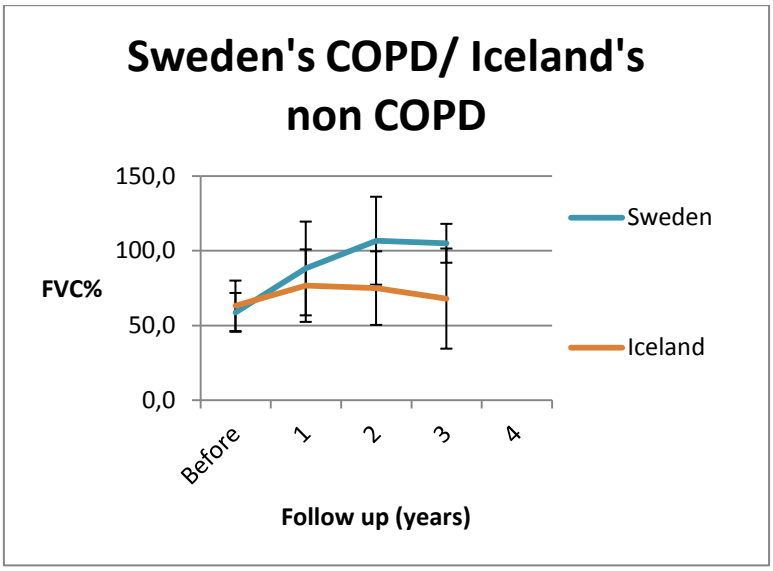

Figure 12 shows four years of follow up of FVC% values of Iceland's non-COPD and Sweden's COPD lung transplant recipients that received a lung transplant in the years 2010–2012. a) Those are Sweden's FVC% values after they were calculated using the American system.

Table 12 Significance of the follow up of FVC% COPD/non-COPD

Follow up	Group	N	Mean	Std. Deviation	Sig.
Second year	Sweden	6	106.7	29.4	.070
	Iceland	6	75.0	24.6	

Table 12 shows the significance of four years of follow up of the comparison of the FVC% values of Iceland's non-COPD and Sweden's COPD lung transplant recipients that received a lung transplant in the years 2010–2012. a) This is the significance of comparison to Sweden's FVC% values after they were calculated using the American system.

4.5 Plasma clearance

As one can see in Figure 13, there is a decline in kidney function after the surgery. In the first year of follow up, Iceland is doing better than Sweden in plasma clearance levels but in the second year

Icelanders are faring worse than in the first year but Sweden is doing better; Sweden remains relatively constant from the second year, but the Icelandic patients are getting better after the second year of follow up. The first year is significant and the 3 year is borderline significant, as shown in Table 13.

Figure 13 Follow up of plasma clearance

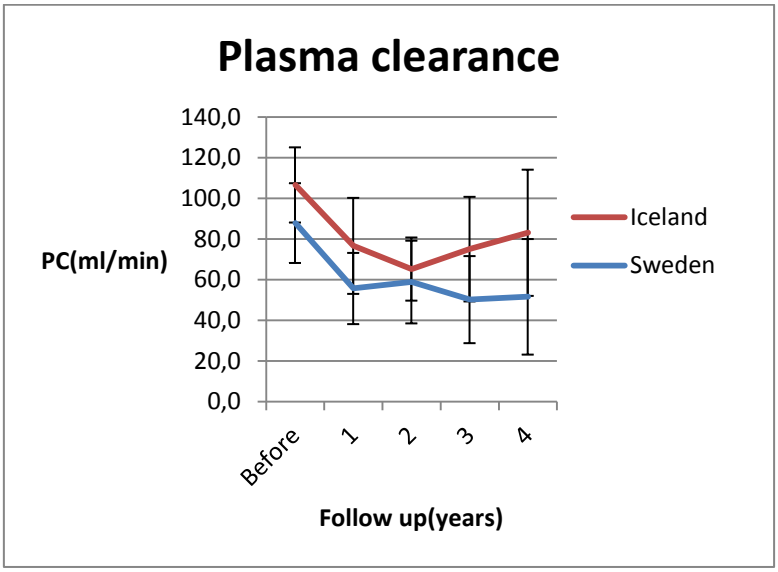

Figure 13 shows four years of follow up of plasma clearance values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012.

Table 13 Significance of the follow up of plasma clearance

Follow up	Group	N	Mean	Std. Deviation	Sig.
First year	Sweden	19	55.7	17.5	.011
	Iceland	10	76.6	23.5	
Third year	Sweden	9	50.2	21.4	.096
	Iceland	4	75.0	25.7	

Table 13 shows the significance of four years of follow up of the comparison of the plasma clearance values of Iceland and Sweden's lung transplant recipients that received a lung transplant in the years 2010–2012

5 Discussion

After looking at survival, the lung function values, the kidney function values, and the stage of BOS, one gets a clearer picture of how these patients are doing after lung transplantation. Additionally, the number of treatments for raised levels of CMV and the occupation status was collected. The patients seem to be doing well on average in every perspective, considering that they had a lung transplantation.

5.1 The matching process

The matching process went fairly well, in that the age and the number of lungs received of the two groups was fairly close; however, the sex ratio was not a complete success along with matching for the indication for the transplant (Table 3). These problems came up because of the trouble with matching perfectly for the Icelandic bronchiolitis patient and the two Icelandic bronchiectasis patients. It wasn't possible to mach one of the Swedish bronchiolitis patients regarding number of lungs received and there was no Swedish bronchiectasis patient that survived for 6 months, so we had to match them to Swedish COPD patients. It is a problem when comparing a single lung transplant patient to a a double lung transplant patient since the one that receives the double lung transplant gains more in lung function. To solve this problem we excluded the lung function values form this patient but nothing else. Picking COPD patients to compare to bronchiectasis is valid, since a big part of COPD patients have bronchiectasis [66].

5.2 EVLP

There is 10% of each group that has EPLV lungs (Table 4). EPLV marks an exciting new era in lung transplantation that will hopefully change the landscape of lung transplantation, but it is too soon to tell. There is a study underway in Sweden looking into the survival of EPLV lungs compared to normal transplantable lungs, but it is only in its first year of follow up and with lung transplant patients' survival being on average 5.5 years, that doesn't really show that EPLV lungs are as good as normal transplantable lungs, but up to this point the results are promising, which will hopefully reduce the mortality rate of patients waiting on the transplant list.

5.3 Survival

The Icelandic patients' survival is better than the Swedish patients' (Table 4), which would point to a better follow up in Iceland for lung transplant recipients; however, this finding is not significant because of the small study population.

5.4 Occupation

There are very few that are working and most lung transplant patients in the Icelandic group are out of work and the majority of Sweden's lung transplant patients have retired (Table 4). This is to be expected because the treatment is hard, with over 10 medications on average [20], and also the

number of patients developing rejection and having rejection with 70% of Iceland's and 50% of Sweden's lung transplant patients (Table 5), which makes it harder for the patients to work since they don't have the same endurance.

5.5 Chronic rejection

That Iceland seems to be doing worse than Sweden with more patients with BOS, developing BOS or RAS (Table 5), is probably not significant due to the small study population. The timing of the development of BOS was almost the same on average—2.1 and 2.2 years—even though Sweden has a little bit more time until BOS develops than Iceland, but the comparison was not significant.

5.6 CMV treatment

More Icelandic patients were treated for raised levels of CMV than their Swedish counterparts, as shown in Table 6. This difference could be explained with different treatments for raised levels of CMV, Iceland possibly treating patients with lower levels of CMV and is probably not significant due to the small study population. The only patient who was treated more than 3 times for raised levels of CMV was the Icelandic mismatched patient. It is known that mismatched patients have a greater risk of raised levels of CMV and therefore an increased risk of developing BOS. The patient should have received six months of treatment at the time that these patients received the transplant (

Table 2), but today the patient would have received 12 months of prophylaxis for CMV infections, which would have probably made the treatments after the prophylaxis fewer. In comparing the number of treatments, one must keep in mind that Sweden doesn't always treat for raised levels of CMV, but rather lowers the dose of immunosuppression so any comparison must be taken with caution.

5.7 Lung function follow up

In FEV1 and FVC, both groups have a marked increase in the values in the first year of follow up compared to before (Figure 1 and Figure 2), but after that they remain relatively constant (Figure 5 and Figure 6). Even though Sweden looks to be doing a lot better, the comparison is not significant.

In FEV1% and FVC%, there is the same marked increase as in FEV1 and FVC in the first year of follow up compared to before (Figure 7 and Figure 8), the difference in FEV1% is borderline significant but is significant in FVC% (Table 7 and Table 8). Also, after the first year, FEV1% and FVC% remain constant, just like FEV1 and FVC (Figure 7 and Figure 8), the mark in change from before the transplant and in the first year is significant in FEV1% and FVC% and the difference between the first year of follow up and the second is borderline significant in FVC% (Table 9 and Table 10).

5.8 Corrected FEV1% and FVC%

The difference between the two patient groups in FEV1% and FVC% (Figure 3 and Figure 4) is not as great after the Swedish FEV1% and FVC% values were calculated again using the American system for reference values.

There is a great difference between the corrected FEV1% and FVC% of Sweden's COPD group compared to Iceland's COPD and non-COPD groups FEV1% and FVC% values (Figure 9, Figure 10, Figure 11 and Figure 12). Even though there is a great difference between Sweden's COPD group and Iceland's COPD and non-COPD groups, only the comparison between Sweden's COPD and Iceland's non-COPD is borderline significant (Table 11 and Table 12).

5.9 Reference values

After noticing the difference in FVC% and FEV1%, it seemed that Icelandic lung transplant recipients were doing much worse according to their lung function; the reason was probably that reference values in the two countries are not the same.

Iceland uses the American system for reference values and Sweden uses the European system for reference values. It might sound strange that Iceland is not using the European system since we are mostly descended from people from Norway and Ireland [67], but that is a question for another study to answer or Iceland could develop its own reference values.

The difference in reference values made it look like Iceland was doing much worse, but after Sweden's FEV1% and FVC% were calculated using the American formula, the difference wasn't as great, especially in the FVC% (Figure 3 and Figure 4).

If the Icelandic lung transplant recipients' FEV1% and FVC% values would have been calculated according to the European system, they probably would have had higher levels of FVC% and FEV1%, but the difference would have probably been the same.

It would have probably been more correct to calculate Iceland's lung transplant patients' FVC% and FEV1% according to the European reference values, because the original values of the Swedish patients probably gives a better clinical picture of their lung function values than the value obtained using the American reference system

But, after correcting for the reference values, there was still a difference and the idea was that FEV1% and FVC% values from the Swedish COPD patients were causing the difference. The reason for this explanation is that in COPD, the thoracic cage expands as the patient tries to catch a breath and could therefore receive bigger lungs than the reference values give indication to. The Swedish COPD patients are doing much better than both Iceland's COPD and non-COPD in FEV1% and FVC%, but the difference is not statistically significant; however, in the non-COPD it is bordering on significance (Table 11 and Table 12).

So, the difference probably stems from the different reference values and the COPD patients receiving bigger lungs than the Icelandic lung transplant recipients did.

5.10 Plasma clearance

Both countries are doing well in the follow up of plasma clearance, but Iceland is doing better (Figure 13). That doesn't have any significance, since the MDRD formula that was used to calculate Iceland's lung transplant patients' plasma clearance values states that all values above 60ml/min should be simply written as above 60 ml/min, not as the actual value. With that said, the only

significant interpretation of the plasma clearance levels is that these patients are on average staying above the clinical line of 60 ml/min.

5.11 Strength and limitations

This is a very small study with only 30 patients, and comparing 10 Icelandic patients to 20 Swedish patients is not ideal. The reason is of course that this is almost half of all lung transplant patients in the history of Iceland (1.2). Another limitation is the timing of this study, with half of the Icelandic lung transplant patients receiving the transplant in 2012 (Table 4), making four years of follow up unlikely to be significant. The strength is that the objective of this study was to rather look at the follow up of these patients rather than the comparison; in that perspective it gives a clear picture.

5.12 Conclusion

What this study could mean for the scientific community is that comparing reference values between the United States and Europe should be done with a caution, since just as the FEV1% and FVC% values in this study show (Figure 3 and Figure 4), the difference can have a great impact.

This study also shows that cooperation between two countries can be beneficial, as Iceland benefits from first of all the lung transplants but also from the help Iceland receives in the follow up of the lung transplant recipients. This help with the follow up is vital for a small country like Iceland that doesn't have the same experience treating lung transplant patients as a large lung transplant center like Sahlgrenska University Hospital in Gothenburg.

This study is unique in that we tried looking at the follow up of lung transplant recipients from two countries and comparing them, and studies to follow up lung transplant recipients in Iceland will always have too few subjects to be significant. That doesn't mean that research such as this one isn't necessary to keep Iceland up with comparable countries such as Sweden. Even though there are few patients in this study, which makes any significance doubtful, it still gives one an idea of the state of the follow up of lung transplant patients in Iceland and shows that with the cooperation with Sweden, Iceland can offer adequate treatment for lung transplant patients.

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