GENDER DIFFERENCES IN SURVIVAL IN IDIOPATHIC PULMONARY FIBROSIS AND FOLLOWING LUNG TRANSPLANT

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Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2007

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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Abstract

Idiopathic Pulmonary Fibrosis (IPF) is a chronic and progressive form of interstitial lung disease characterized by inflammation and abnormal tissue repair ultimately leading to decreased pulmonary function and death. Risk factors for IPF are largely unknown and medical treatment offers a poor prognosis due to the lack of effective treatment options.

Survival outcomes were analyzed for a cohort of 331 patients. The median age at clinical evaluation for IPF was 69 years. Subjects survived an average of 21.82 months after diagnosis, with a higher survival in females than in males. Males had a risk 2.85 times higher than females of death. Subjects older than 69 years of age had a relative risk of dying of 1.6 in comparison to subjects younger than 69 years.

Predictors of survival after lung transplant were also analyzed in a cohort of 990 lung transplanted patients. The overall survival was 41.6%, (41.5 % in males, and 41.8 % in females), the average length of the follow up was 45.84 $\pm$ 51.98 months (range 0 to 282.47 months). Females tend to live longer than males: 50.75 $\pm$ 55.41 months versus 40.64 $\pm$ 47.60 months respectively. Males had a risk of dying during the follow up that was 1.18 (95% CI 1.01-1.40) relative to females, after adjusting for ethnicity, age, smoking status, diagnosis and donor characteristics. Females who had at least one full term pregnancy during their life had better survival rates than females who had no full term pregnancies.

Our results of a better survival after lung transplant in females (particularly females with at least one pregnancy) support the hypothesis of a hormonal contribution to survival and of the development of immunotolerance after pregnancy.

The public health significance includes the use of the current study as a model in understanding the role of immunity in cancer development. The age-adjusted incidence rate is 555.8 per 100,000 men and 411.3 per 100,000 women per year (2000-2004), and the combined lifetime risk of cancer is approximately 1 in 2. Thus, any further understanding of cancer causes would be worthwhile in cancer prevention and treatment efforts.

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1.0 INTRODUCTION

1.1 INTERSTITIAL LUNG DISEASE

Interstitial lung disease consists of a group of lung disorders (Appendix A) characterized by dyspnea, diffuse parenchymal lung infiltrates, restrictive airway pattern, and diminished gas exchange. The most common type of interstitial lung disease is idiopathic pulmonary fibrosis (IPF) [1]. IPF is a chronic and progressive form of interstitial lung disease characterized by inflammation and abnormal tissue repair (scarring). Scarring consists of replacement of normal lung tissue with connective tissue, including collagen [2].

1.2 IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis is a progressive and ultimately fatal disease [3]. While the exact mechanisms for the development of IPF are unknown, it is widely believed that chronic inflammation is the underlying cause. Repeated injury to alveoli is believed to result in alveolar basement membrane damage. Physiological attempts to repair the basement membrane lead to an exudative process of macrophage and fibroblast recruitment within the alveolar spaces over time. Inflammatory cell recruitment and additional neovascularization results in alveolar

airspace destruction and loss of alveolar architecture. Eventually, progressive fibrosis results as increased fibroblasts lead to collagen production and creation of extracellular matrix [3].

2.0 EPIDEMIOLOGY

2.1 PREVALENCE

The prevalence of IPF is not well defined, but ranges from 3 to 29 cases per 100,000 [1]. A study in Bernalillo, New Mexico revealed a prevalence of 20.2 cases per 100,000 for males and 13.2 cases per 100,000 for females with IPF [4]. More cases of IPF have been reported in males; the ratio of IPF in males to females is estimated to range from 1:1 to 2:1 [1]. Approximately two-thirds of patients worldwide with IPF were older than 60 at the time of presentation (mean age of diagnosis 66 years) [5].

2.2 SURVIVAL

The mean survival of IPF ranges from 2 to 4 yr (5-yr survival range, 30 to 50%) [4]. The median survival of IPF at three years is 50% [6]. For comparison, the median survival for COPD (FEV1 < 30% predicted) is 50% at 3 years and the median survival for lung cancer is 85% at 5 years. Thus, the prognosis of interstitial pulmonary fibrosis is very poor, even in comparison to lung cancer. Older age at diagnosis of IPF leads to a poorer outcome, as does male gender, and certain radiographic findings (including the predominance of reticular abnormality or honeycombing on HRCT) [6].

3.0 RISK FACTORS

3.1 GENERAL

Risk factors for poor outcome of patients with IPF include older age, cigarette smoking, and male gender. Death from IPF is more common in males and increases with age [6, 7]. Survival in IPF is shorter in men compared to women and the possibility of a gender difference, possibly genetic or hormonal, has been suggested [8], however, a paucity of data exists to illuminate the potential etiology of gender differences.

3.2 SMOKING

Cigarette smoking may augment the inflammatory process in IPF and is believed to enhance the rate of disease progression in IPF [9]. A high percentage of persons with IPF are smokers [10]. In one study, a history of ever smoking was associated with a 60% increased risk for development of IPF [10].

3.3 ENVIRONMENTAL EXPOSURES

In addition to smoking, other occupational or environmental risk factors for IPF include working with livestock and exposure to wood dust [7]. Intrapulmonary deposition of hazardous dusts, especially metallic dusts, appears to play at least a partial role in initiating IPF [11]. Other associations with IPF have been implied such as Epstein Barr virus (EBV) and other environmental exposures including mineral dust (silica) [7, 10]. However, the majority of individuals sharing an environment do not develop IPF, suggesting a genetic predisposition [7] which has yet to be determined.

4.0 TREATMENT

4.1 GENERAL

The currently available medical treatments consist mainly of immunosuppressants, such as steroids and cytotoxic agents, which offer a poor prognosis for IPF patients. Utilization of corticosteroids and/or immunosuppressive agents have been unsuccessful in the treatment of IPF and have not improved disease survival period [5]. The end-stages of IPF are characterized by severe pulmonary hypertension with cor pulmonale that often dose not improve with oxygen therapy [5]. The American Thoracic Society recommends that patients with significant deterioration should be considered for lung transplantation [4].

4.2 TRANSPLANTATION

Lung transplantation is recognized as a treatment option for patients with IPF. Transplantation can prolong life and improve quality of life in end-stage patients with severe respiratory insufficiency and who have failed medical treatment. Single lung transplantation results in an actuarial survival of 73% at one year and 57% at three years [12]. Old age, concurrent medical conditions, and issues inherent to transplant (including shortage of donor organs and rejection) often preclude lung transplant as a treatment option.

While current medical treatments offer a poor prognosis, lung transplantation has been demonstrated to have a median survival of approximately 36 months in IPF patients [13]. Transplant often leads to improved lung function and exercise capacity and improved perception of quality of life; many transplant recipients are able to return to work in comparison to those patients who do not undergo transplant [14].

However, limitations for lung transplantation exist including the lack of available donor organs with waiting times being as much as 2 years or more [14]. Candidates for transplant must also meet strict criteria.

4.2.1 *Transplant Rejection*

The most common reason that lung transplant fails to be a more successful treatment in the long term is organ rejection. One of the most common causes of organ rejection is fibrosis. Primarily, chronic lung rejection that is characterized by bronchiolitis obliterans syndrome (BOS) has become a major obstacle for the long-term survival of lung allograft recipients [12]. Constrictive BOS is a rapidly progressive inflammation disorder of the small airways that causes severe airflow restriction. The cause of BOS is believed to be repetitive episodes of acute rejection which lead to repeated inflammation and repair with excessive proliferation of granulation tissue and fibrosis [15]. Other risk factors postulated to contribute to BOS include chronic rejection directed against bronchiolar epithelium, CMV infection, and recipient/donor difference in HLA antigens leading to post-transplant HLA-antibody production [16]. One year after transplantation, approximately 30% of deaths are due to BOS and as many as 50% of lung recipients will have had BOS within 5 years after transplantation [14].

5.0 IMMUNOLOGY

While the specific causes of IPF are unknown, it is well documented that various cytokines in the immune system have significant effect in the progression of fibrosis. Various cytokines, chemokines, and immune mediators have been shown to play a role in the progression of pulmonary fibrosis. Tumor growth factor beta-1 (TGF-β1) has a role in inflammation and connective tissue synthesis. Interleukin-1 has been shown to increase pulmonary fibrosis as well as increasing the levels of TGF-β1. TGF-β1 is a critical cytokine in the inflammatory and immune response involved in lung fibrosis and is believed to be the central mediator of tissue repair and fibrosis. TGF-β1 is a chemotactic factor for fibroblasts, monocytes, and macrophages. TGF-β1 can induce the expression of itself, affects proliferation of epithelial cells, and induces epithelial cells to create connective tissue [17]. Monocytes and macrophages produce many of the key cytokines, but also TGF-β1. Fibroblasts make collagens, glycosaminoglycans, reticular and elastic fibers, and glycoproteins found in the extracellular matrix creating the fibrotic network. TGF-β1 is likely a critical immune modulator in IPF being found at levels 11-fold higher in IPF patients compared to control lung [18].

IPF is a chronic and progressive disease with limited prospect for cure. Primary medical treatment consists of immunosuppressive therapies while surgical treatment is primarily lung transplant. Medical therapy attempts to target the immune system mediators such as cytokines

and surgical therapies attempt to limit the host immune response thereby minimizing allograft rejection. The immune system is the architect of the fibrosis of IPF as repetitive inflammatory responses lead to progressive collagen deposition and fibrosis ultimately leading to lung tissue that is too restricted to ventilate.

6.0 GENDER

6.1 GENDER AND IMMUNOLOGY

Much research and discussion has revolved around the immunological involvement in IPF, but little exploration into gender differences in the disease itself and as it relates to immunology exist.

Women have a higher incidence of immunologically based illnesses (e.g. Systemic Lupus Erythematosus and Grave's Disease) and have greater immune reactivity than males [2, 19]. Cell-mediated immunity and natural killer (NK) cell activity are diminished during pregnancy, and menopausal women have increased release of interleukin-1 (IL-1) by monocytes [19]. In addition, many of the components of immune regulation are affected by circulating levels of estrogen.

In kidney transplantation, women over 45 years of age have a decreased relative risk of chronic allograft failure in comparison to younger women and men, however, women have a higher relative risk of acute rejection [19].

Experiments in which pulmonary fibrosis was induced in rats with bleomycin show that female rats had increased susceptibility to develop lung fibrosis and had higher mortality rates than males [2]. The female rats had higher levels of collagen precursors in lung tissue than males indicating greater lung inflammation and fibrosis, however, when the ovaries of the female

rats were removed (i.e. removing the source of estrogen), morbidity, mortality, cytokine expression, and fibrosis were diminished indicating that gender differences may, in fact, be related to hormonal differences [2].

6.2 PREGNANCY

A Polish study indicates that pregnancy and lactation may be protectors of cell-mediated immunity as women age. Multiparous elderly women (mean age 74) had a stronger lymphocyte reaction compared to nulliparous elderly women (mean age 77) and were, in fact, similar in immune reaction to young nulliparous women (mean age 26) [20]. T-cells differentiate and mature in the thymus. Lactation following pregnancy increases prolactin levels in the female human and mouse. The prolactin acts on immunocytes that promote the generation of thymus tissue, thus increasing the ability of immune cells to mature and circulate in the body; the process may be responsible for the long-lasting immunoenhancing effect of multiparity and lactation [20].

Pregnancy may confer protection against disease via hormonal changes or by increasing immunity through introduction of fetal antigens. Pregnancy has been theorized to provide a protective effect in breast cancer as a result of changes in estrogen fractions during early reproductive life [21]. Additionally, the fetal antigen hypothesis has been a proposed mechanism by which women are naturally immunized against cancer antigens by antigens from their fetuses [22]. It could be possible that multiparity may further increase anti-antigen/antibody diversity through the introduction of different antigens (such as novel genetic material) with subsequent births. Studies have provided evidence that pregnancy provides immunization to antigens found

in breast, ovarian, and endometrial cancer cells possibly due to protection gained from exposure to fetal antigens [22, 23]. Fetal-maternal immunization against cancer is a hypothesis that may be a possible answer to the gender differences in IPF as exemplified by the lower incidence of IPF in women as compared to men. Thus, pregnancy may provide a protection mechanism, whether hormonal or immunological, for women against IPF.

7.0 SURVIVAL OUTCOMES IN IDIOPATHIC PULMONARY FIBROSIS

7.1 MATERIALS AND METHODS

The data were extracted from patient records at the Simmons Center for Interstitial Lung Diseases at UPMC. All consecutive patients who referred to the Center for further evaluation and treatment, and had a diagnosis of Idiopathic Lung Fibrosis from 1982 to 2006 were included in this analysis (n=331). Demographics (gender, ethnicity, age at evaluation, smoking status) and clinical (Forced Vital Capacity - FVC and Diffusing Capacity of the Lung for Carbon Monoxide - DL_{CO}) were extracted from an anonymous data set prepared for this purpose.

DL_{CO} is the rate of uptake of carbon monoxide (CO) per driving pressure of alveolar CO, and provides an objective measurement of lung function; FVC is the volume change of the lung between a full inspiration to total lung capacity and a maximal expiration to residual volume. For the purpose of this analysis, former and current smokers have been included in one category, called ever smokers.

Information on patients' follow up included the date of their last clinical visit, or the date of death or the date of loss at follow up, whichever came first.

All patients signed an informed consent to be included in a research registry.

7.2 STATISTICS

Categorical data are presented as frequencies, continuous variables as means and Standard Deviations. The statistical endpoint for survival analysis was death, while the time frame for this analysis was the date at initial evaluation at the Simmons Center for Interstitial Lung Diseases at UPMC (diagnosis of IPF) and the date of death or date of current status (November 10, 2006).

Crosstabulations were created to identify relationships between variables via 2x2 tables.

Pearson Chi-square was used to test for the significance of the relationship between variables associated with death. Kaplan-Meier plots were generated to study the determinant of survival. Univariate and multivariate hazard ratios with confidence intervals were calculated using maximum-likelihood proportional hazard models. This analysis allows the independent contribution of several factors (age at diagnosis, gender etc) to the risk of death. All statistical analyses were done using Intercooled Stata (Version 8.2; Stata Corp LP, College Station, TX).

7.3 PARTICIPANTS

The study population (n = 331) included 201 males and 130 females, 313 of whom were Caucasians. The age at clinical evaluation for IPF ranged from 27 to 88 years of age, with a median of 69 years. Most of the patients were former smokers (n=218), with a large variability in their pulmonary function parameters at entry. At the time of this data collection and analysis, 146 patients were known to be deceased.

Table 1 Demographic Characteristics of Participants (n=331)

Variable	N	%
Gender		
Male	201	60.7
Female	130	39.3
Ethnicity		
Caucasian	313	94.6
Other/Unknown	18	0.4
Smoking Status		
Current	7	2.1
Former	218	65.9
Never	95	28.7
Unknown	11	3.3
	Means ± SD	**Range**
Age at Evaluation	68.02 ± 9.57	27.5-88.6
FVC (liters)	2.26 ± 0.86	0.56 - 4.96
DL_{CO} *(mlCO/min/mmHg)*	9.74 ± 4.42	2.77-31.7

7.4 SURVIVAL ANALYSIS

The overall survival of the population according to gender is reported in Figure 1. Subjects survived an average of 21.82 months (SD: 18.22 months) after diagnosis, with a higher survival in females (23.43 months) than in males (20.78 months).

The univariate analysis (Table 2) shows that the effect of gender on survival is more pronounced in subjects younger than 69 years of age then in those 69 or older. In younger subjects, each incremental[1] increase in age corresponds to a 3% increased risk of death during the follow up. Other variables associated with survival were the pulmonary function parameters at entry.

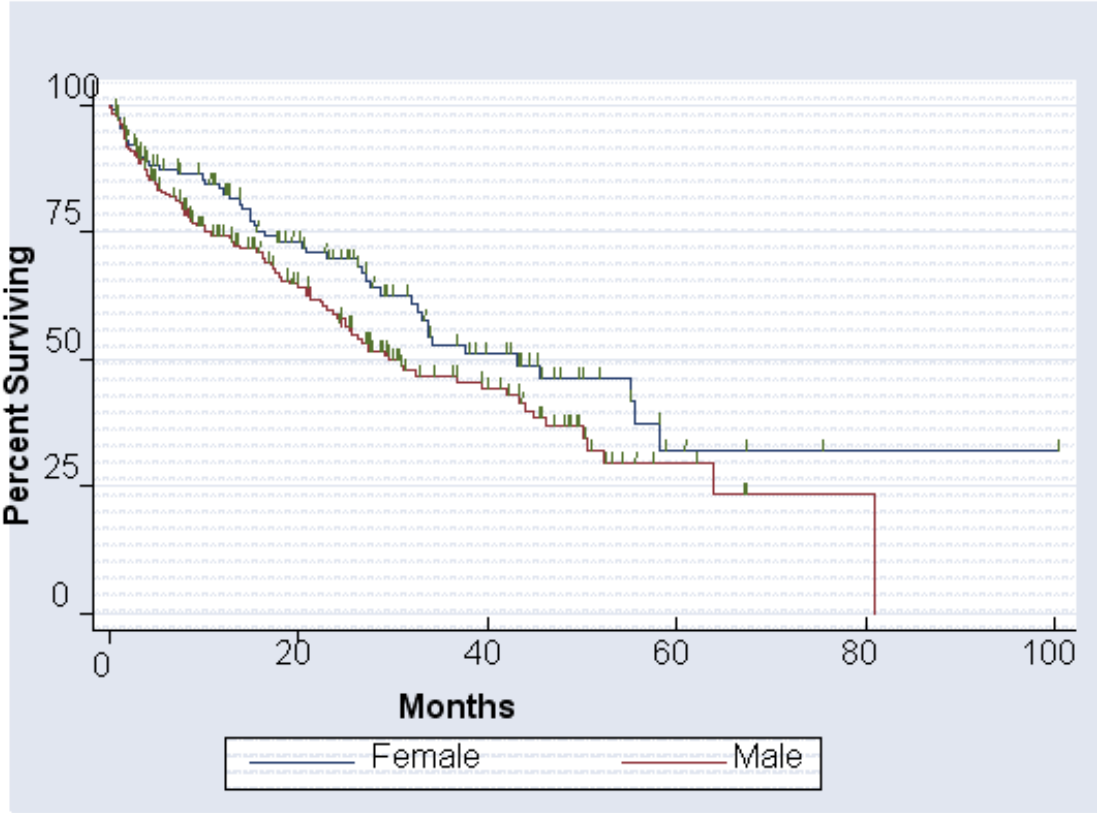

Figure 1 Kaplan-Meier overall survival estimates by gender

The multivariate analysis shows that the independent factors contributing to survival are age at diagnosis, gender, and the parameters of pulmonary function at entry.

[1] Incremental increases are any difference in age between study participants

Males have a risk 2.85 times higher than females of dying during the follow up, after controlling for age, pulmonary function, smoking and ethnicity. Subjects ≥ 69 years of age have a relative risk of dying of 1.6 in comparison to subjects younger than 69 years (Table 3).

Table 2 Association between selected variables and survival

Univariate analysis		
Variable	**Hazard Ratio**	**95% Conf. Interval**
Gender	1.38	1.0, 2.0
Gender if age < 69 at evaluation	1.59	1.0, 2.7
Gender if age ≥ 69 at Evaluation	1.23	0.8, 1.9
Ethnicity	1.28	0.5, 3.5
Smoking_status	0.98	0.7, 1.4
Age at Evaluation *	1.03	1.0, 1.0
FVC at Evaluation *	0.71	0.6, 0.9
DLCO at Evaluation*	0.91	0.9, 1.0

* Continuous variable

Table 3 Association between selected variables and survival

Multivariate Analysis		
Variable	**Hazard Ratio****	**95% Conf. Interval**
Gender (males/females)	2.85	1.7, 4.7
Age at Evaluation (≥ 69 vs < 69 yrs)	1.60	1.1, 2.4
FVC at Evaluation (liters)*	0.64	0.5, 0.9
DL_{CO} *(mlCO/min/mmHg)* *	0.90	0.8, 1.0

** Adjusted for smoking and ethnicity

* Continuous variable

8.0 PREDICTORS OF SURVIVAL AFTER LUNG TRANSPLANT

8.1 INTRODUCTION

Results of clinical lung transplantation over the past two decades have progressively improved. However, lung transplant is still characterized by a low 5 year survival, as shown by various international data [24]. Single lung transplantation results in an actuarial survival of 73% at one year and 57% at three years [12].

A re-analysis of the United Network for Organ Sharing (UNOS) database showed comparable short- and midterm survival for bilateral versus single lung transplants in patients 60 years of age or older. Predictors of survival in this population were smoking and history of idiopathic pulmonary fibrosis [25].

It has been suggested that donor-recipient gender combination may affect lung transplant survival, with a selective advantage for female to female transplant [26]. Several hypotheses have been put forward in order to explain these differences, for example the role of female hormones in increasing immuno-response and wound healing [27-31].

Full term pregnancy is also responsible for changes in both hormonal and immuno responses [19, 21-23]. However, the role of full term pregnancies on transplant survival in females has never been considered.

Understanding the regulation of immune responses in pregnancy may lead to new therapeutic concepts in transplanted patients. The model could also be very useful in order to understand cancer etiopathogenesis, since mechanisms physiologically used for induction of tolerance by the fetus are frequently abused by pathogens or tumors intending to escape the host's immune response [32].

A series of consecutive lung transplant patients have been analyzed in order to establish: a) if gender gives a selective advantage for survival after lung transplant, and b) if this advantage can be partly explained by full term pregnancies.

8.2 MATERIALS AND METHODS

This study was conducted on all consecutive patients who underwent a lung transplant at the University of Pittsburgh from May 28, 1982 to February 2, 2007. Subjects with single lung, double lung and combined heart-lung transplant were included. There were 414 double lung transplants, 121 heart-lung transplants, and 445 single lung transplants. Demographics of the recipient (gender, ethnicity, age at transplant, smoking status), as well as the pathology underlying the need for a transplant were extracted from an anonymous data set prepared for this purpose. For females, we were able to gather information on a number of full term pregnancies.

Six transplants were from living donors while the remainders were transplanted from cadaveric donors. Age and gender of the donor was also available.

Information on patients' follow up included the date of their last clinical visit, or the date of death or the date of loss at follow up, whichever came first. All patients have signed an informed consent to be included in a research registry.

Subjects underwent lung transplant for several underlying pathologies that were summarized into 7 groups for the purpose of this study. Pulmonary hypertension includes both primary and secondary hypertension, the latter being caused being secondary to a congenital heart defect. Lung fibrosis includes both primary lung fibrosis and lung fibrosis secondary to chemotherapy. All the connective tissue disorders were included in one group.

8.3 STATISTICAL ANALYSIS

Categorical data are presented as frequencies, continuous variables as means and Standard Deviations. The statistical endpoint for survival analysis was death, while the time frame for this analysis was the date at lung transplant, the date of death or date of current status (as of February 14, 2007).

Cross-tabulations were created to identify relationships between variables via 2x2 tables.

Pearson Chi-square was used to test for the significance of the relationship between variables associated with death. Kaplan-Meier plots were generated to study the determinant of survival.

Univariate and multivariate hazard ratios with confidence intervals were calculated using maximum-likelihood proportional hazard models. This analysis allows the independent contribution of several factors (age at diagnosis, gender etc) to the risk of death. All statistical analyses were done using Intercooled Stata (Version 8.2; Stata Corp LP, College Station, TX).

8.4 RESULTS

The population under study consisted of 990 lung transplanted patients. The characteristics of the subjects are reported in Table 4. The majority of the patients were Caucasians; the proportion of males was roughly half, and so was the proportion of subjects who were never smokers, with a variety of pathologies behind their transplant. Seventeen percent of the subjects suffered of emphysema or pulmonary hypertension, while roughly 15% underwent the transplant because of pulmonary fibrosis, either primary or secondary to a congenital heart disease.

Table 4 Demographic Characteristics of Participants (n=990)

Variable	**N**	**%**
Gender		
Male	481	48.6
Female	509	51.4
Ethnicity		
Caucasian	886	89.5
African American	48	4.9
Other	45	4.6
Smoking Status †		
Never	502	50.6
≤34.5 Pack Yrs	244	24.7
>34.5 Pack Yrs	244	24.7
Diagnosis Categories		
Pulmonary Fibrosis	149	15.1
COPD/ Emphysema	268	27.0
Cystic Fibrosis	134	13.5
α-1-Antitrypsin Def.	74	7.5
Pulmonary Hypertension	173	17.5
CREST, sclerodermia, sarcoidosis, connective tissue disorders	81	8.2
Others*	111	11.2

† Smokers divided into two groups based on median pack years of smoking

* Others include: Bronchiectasis, Bronchoalveolar Cancer, BOOP, Obliterative Bronchiolitis, Graft vs. Host, Retransplant, Silicosis, Lymphangioleiomyomatosis, Dilated Myopathy: Ischemic or idiopathic, Eosinophilic Granuloma, Pulmonary embolism

8.5 SURVIVAL ANALYSIS

The overall survival was 41.6%, (41.5 % in males, and 41.8 % in females), the average length of the follow up was 45.84 ± 51.98 months (range 0 to 282.47 months). Females tend to live longer than males: 50.75 ± 55.41 months (range 0 to 262.5 months) versus 40.64 ± 47.60 months (range 0 to 282.47 months) respectively (Figure 2).

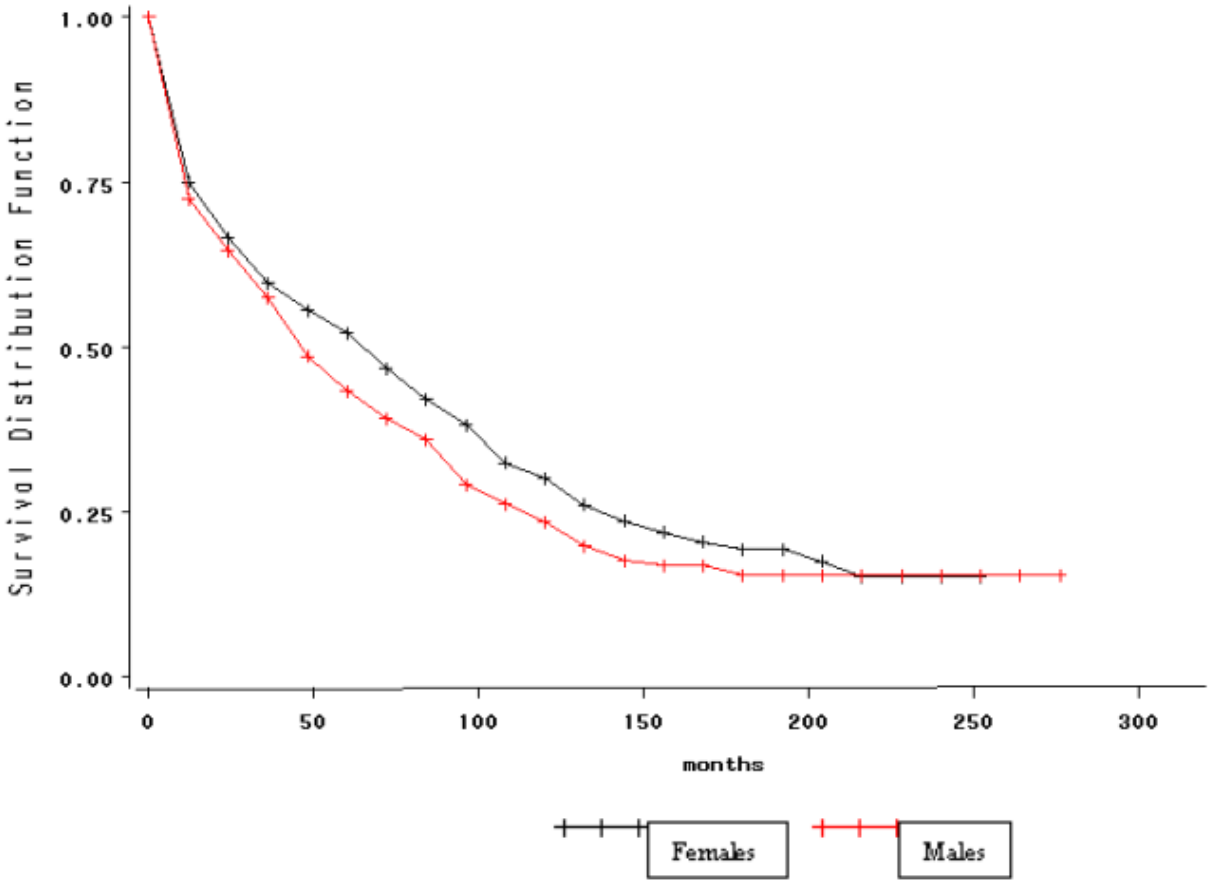

Figure 2 Post–transplant survival according to gender

Post-transplant survival curves are presented in Figure 3. The average survival of the all population was 50.1 months, with variability among pathologies. Pulmonary hypertension and α-1-Antitrypsin Deficiency were associated with the lowest five years survival, while emphysema and COPD were the pathologies with the highest five years survival (Table 5). Patients with lung fibrosis survived an average of 33.75 months after lung transplant, while patients with pulmonary hypertension survived 57.42 months on average.

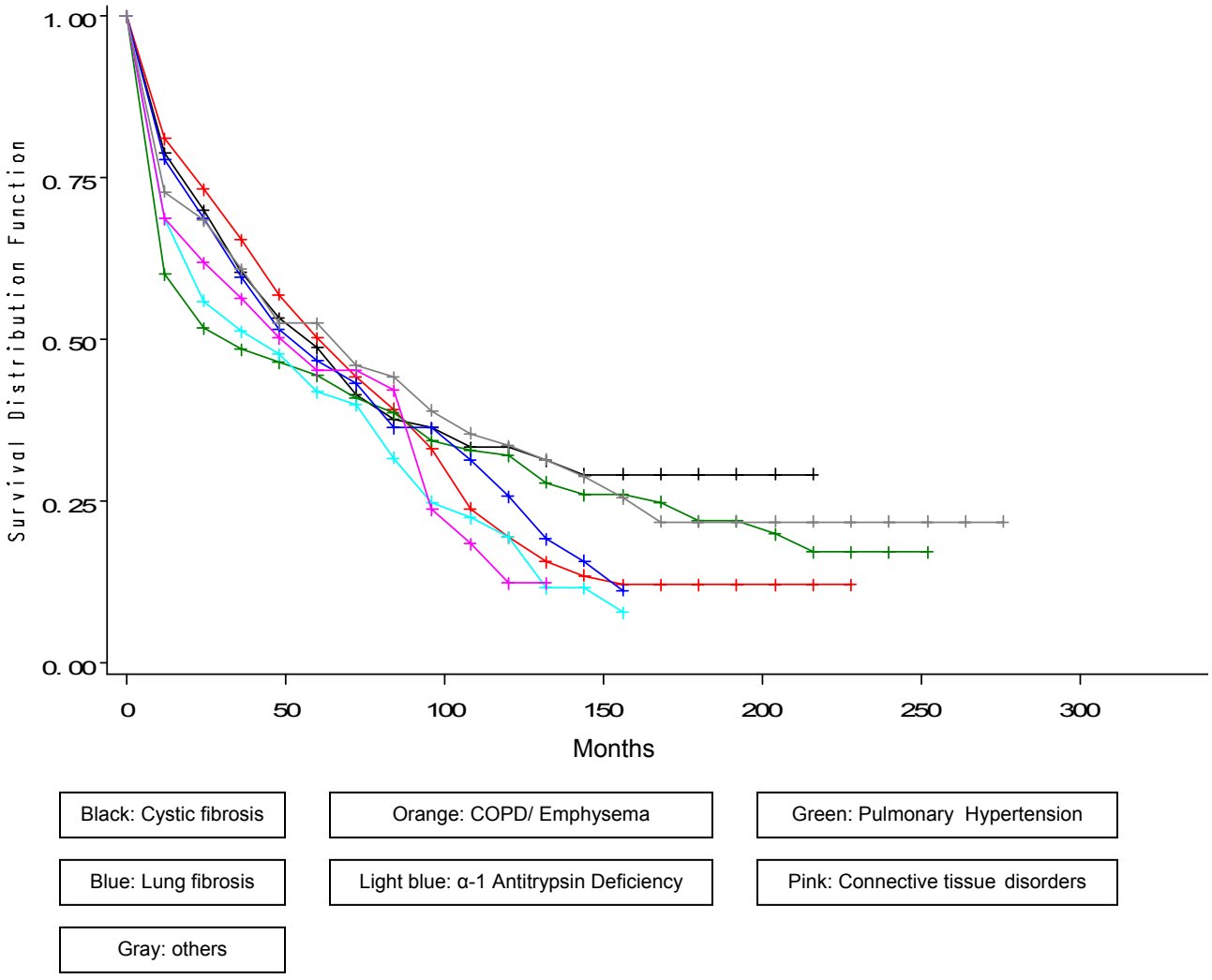

Figure 3 Post–transplant actuarial survival curves according to underlying diagnosis

Table 5 Survival of patients undergoing lung transplant (according to diagnosis and gender)

Diagnosis	5 year survival	Overall survival in months mean ± SD (range)
Cystic Fibrosis	53%	50.07 ± 54.73 (0- 222.67)
COPD/Emphysema	57%	46.85 ± 44.34 (0 - 239.27)
Pulmonary hypertension	46%	57.42 ± 70.87 (0 - 262.50)
Lung fibrosis	52%	33.75 ± 38.11 (0 - 161.87)
α-1 antitrypsin deficiency	48%	42.75 ± 44.31 (0 - 166.77)
Connective tissue disorders	50%	32.40 ± 35.94 (0.2 - 139.13)
Others	53%	48.31 ± 57.25 (0 - 282.47)
Gender		
Male	43%	40.64 ± 47.60 (0- 282.47)
Female	52%	50.75 ± 55.41 (0 - 262.5)

Among the variables considered as predictors of survival, gender and ethnicity resulted to be significantly associated with outcome.

Males had a risk of dying during the follow up that was 1.18 (95% CI 1.01-1.40) relative to females, after adjusting for ethnicity, age, smoking status, diagnosis and donor characteristics. The hazard ratio was 1.43 (95% CI 1.17-1.65) for Caucasians versus African Americans and Others (Table 6).

Females who had at least one full term pregnancy during their life had better survival rates than females who had no full term pregnancies (Figure 4).

Table 6 Independent contribution of several variables to the overall survival

Variable	Hazard Ratio	95% Confidence Interval
Gender (males/females)	1.18	1.01-1.40
Ethnicity (Caucasians/African Americans/others)	1.40	1.17-1.65
Smoking (>34.5 pk-yrs/≤ 34.5 pk-yrs/never)	0.96	0.85-1.08
Age recipient (> 49.5/≤49.5 years)	1.02	0.84-1.25
Diagnosis (7 categories)	1.00	0.97-1.07
Donor/recipient gender match	1.02	0.92-1.14
Age donor (> 49.5/≤49.5 years)	1.01	0.97-1.05

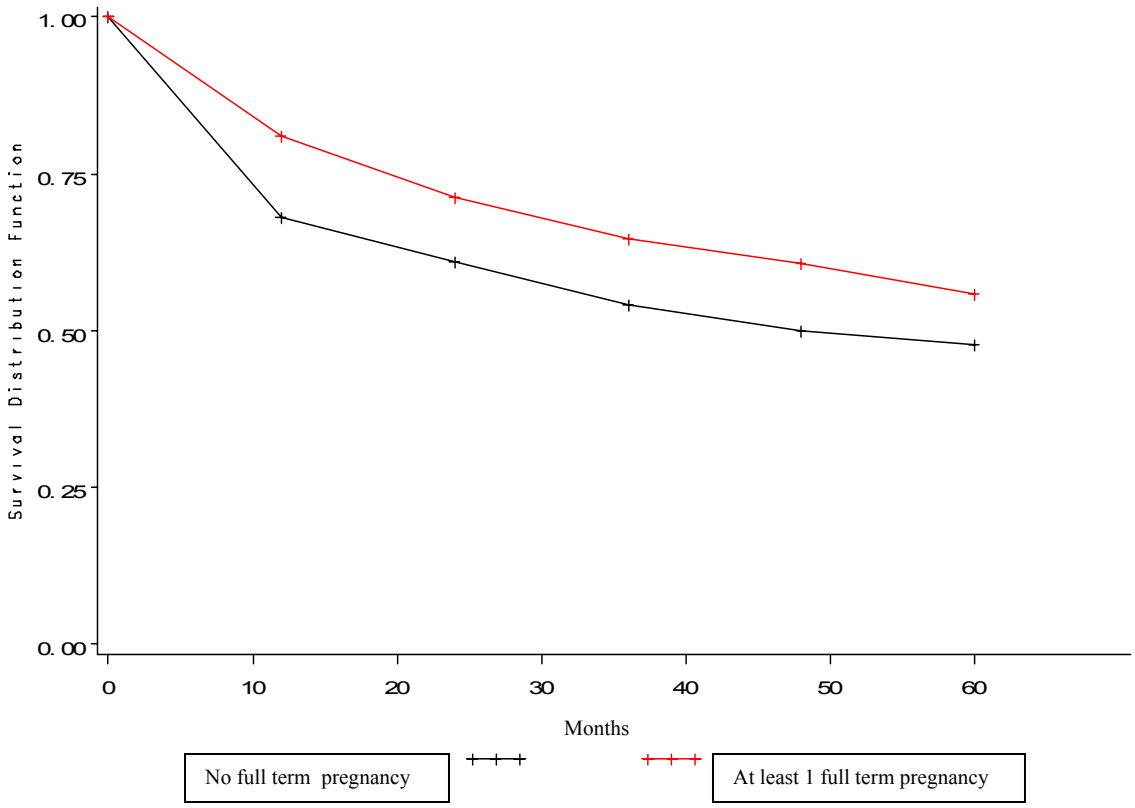

Figure 4 Post-transplant actuarial survival curves according to pregnancy history

8.6 DISCUSSION

The statistical analysis of the IPF study group indicates that gender and age at evaluation are significant risk factors for mortality due to IPF. Specifically, the present study found that men have a greater risk of death due to IPF, which is consistent with prior research [1, 8, 33]. Prior studies [9, 10] have suggested that smoking is a potential risk factor for death in IPF

patients, however, smoking was not found to be a statistically significant risk factor in the present study population.

Smoking appears to have no statistically significant effect on outcome in women less than age 69 at age of evaluation for IPF in the present cohort. The cause of death for this age group could be dependent on variables that have been postulated by other researchers, i.e. hormones, parity. Subsequent investigations may elucidate potential causative factors in IPF outcome.

In order to answer the question as to why gender and age play a role in IPF mortality, certain information must be ascertained. Other studies have suggested that hormones and/or parity in women may play a protective role in females; however, a study with sufficient data does not yet exist. A study of IPF patients accounting for pregnancies and/or hormone levels is required to provide insight into the gender differences in the mortality of IPF patients. Serum hormone levels and documented history of parity in women would be necessary study variables.

The study on a large series of well-characterized lung transplanted patients demonstrates that females have significantly better survival than males. The result holds true after adjustment for several potential confounding factors, for example smoking and underlying pathology. In addition, women who carried at least a full term pregnancy in their lifetime have better survival than women who did not.

The reasons for these preliminary observations need to be analyzed more in depth, but hypotheses for the differences in survival with gender and with full term pregnancy among women can be put forward.

Pregnancy is associated with hormonal changes and immunotolerance through introduction of fetal antigens. It is known that pregnancy provides a protective effect towards

breast cancer, and this protection has been attributed to changes in estrogen fractions and levels during early reproductive life [21]. Many of the components of immune regulation are affected by circulating levels of estrogen, thus linking the hormonal with the immunological hypothesis.

The fetal antigen hypothesis has been a proposed mechanism by which women are naturally immunized against cancer antigens by antigens from their fetuses [22], and could apply to immunotolerance to solid organ transplants as well. It could be possible that multiparity may further increase anti-antigen/antibody diversity through the introduction of different antigens (such as novel genetic material) with subsequent births. Cell-mediated immunity and natural killer (NK) cell activity are diminished during pregnancy, and menopausal women have increased release of interleukin-1 (IL-1) by monocytes [19].

Studies have provided evidence that pregnancy is associated with the development of immunization to antigens found in breast, ovarian, and endometrial cancer cells possibly due to past exposure to fetal antigens [22, 23]. For example, it has been shown that early age at first birth, cycle lengths ≥ 30 days, and oral contraceptive use increased the likelihood of having anti-MUC1 antibodies, a glycoprotein overexpressed in ovarian cancer [34].

Our results of a better survival after lung transplant in females, and among them in those who had at least a full term pregnancy support the hypothesis of a hormonal contribution to survival and of the development of immunotolerance after pregnancy.

Unfortunately, no data on hormonal levels or on detailed reproductive history are available in this or other studies on transplanted patients. Concerted efforts to create a prospective study which include detailed parity history and hormonal levels of the participants in further studies in this direction are warranted, in order to understand the mechanisms of immuno

tolerance to a foreign body. This will help in developing a model for understanding the role of immunotolerance in cancer development.

The age-adjusted incidence rate (2000-2004) of all types of cancer was 555.8 per 100,000 men and 411.3 per 100,000 women per year [35] and the lifetime risk of cancer is 1 in 2. Thus, any knowledge to further delineate the etiopathology of cancer causes would be worthwhile in prevention and treatment efforts and provide a significant benefit to public health.

APPENDIX A

CLASSIFICATION OF INTERSTITIAL LUNG DISEASES

Occupational and Environmental Diseases
Silicosis
Asbestosis
Hard-metal pneumoconiosis
Coal worker's pneumoconiosis
Berylliosis
Hypersensitivity Pneumonitis
Bird breeder's lung
Farmer's lung
Connective Tissue Diseases
Systemic lupus erythematosus
Scleroderma
Rheumatoid arthritis
Dermatomyositis
Ankylosing spondylitis
Primary Diseases
Sarcoidosis
Broncholaveolar carcinoma
Pulmonary lymphoma
Acute respiratory distress syndrome
Postinfectious
Treatment-Related or Drug-Induced Diseases
Antibiotics (nitrofurantoin, sulfasalazine)
Antiarrhythmics (amiodarone, tocainide, propranolol)
Anti-inflammatories (gold, penicillamine)
Anticonvulsants (dilantin)

Chemotherapeutic agents (mitomycin C, bleomycin, busulfan, cyclophosphamide, chlorambucil, methotrexate, azathioprine, BCNU [carmustine], procarbazine)
Therapeutic radiation
Idiopathic Fibrotic Disorders
Idiopathic pulmonary fibrosis
Respiratory bronchiolitis
Lymphocytic interstitial pneumonia (Sjögren's syndrome, connective tissue disease, AIDS, Hashimoto's thyroiditis)
Autoimmune pulmonary fibrosis (inflammatory bowel disease, primary biliary cirrhosis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia)
Other
Bronchiolitis obliterans with organizing pneumonia (BOOP)

Adapted from:

Mason RJ, Broaddus VC, Murray JF, Nadel JA, editors. *Mason: Murray & Nadel's Textbook of Respiratory Medicine.* 4th ed. Philadelphia: Elsevier Saunders; 2005

Reynolds HY. Diagnostic and Management Strategies for Diffuse Interstitial Lung Disease. *Chest* 1998;113: 192-202

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