

Lung Transplantation in Cystic Fibrosis Patients

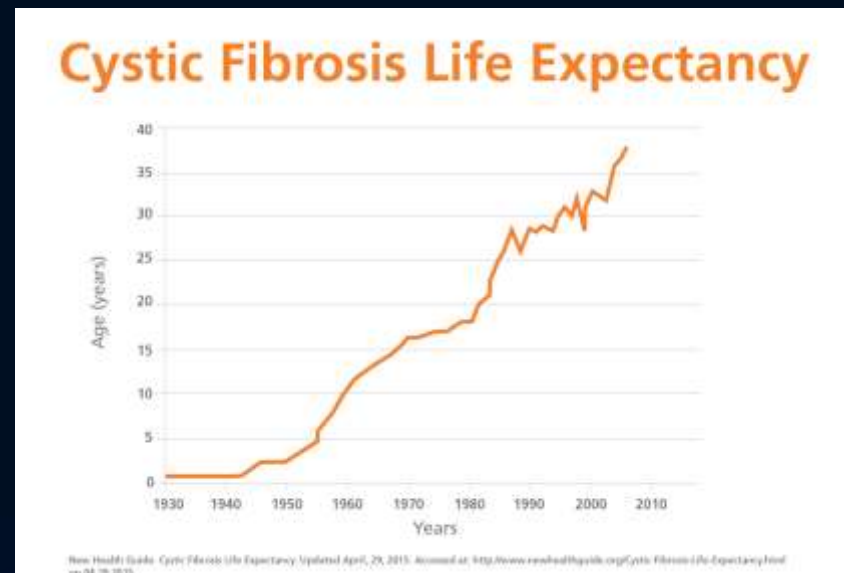
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CF ISRAELI CONFERENCE 2015

'Beginning of new era' in the treatment of cystic fibrosis

- Cystic fibrosis is a life-threatening disease, but we are living in a new era with huge progress in treatment options.
- As a result, life expectancy is increasing...



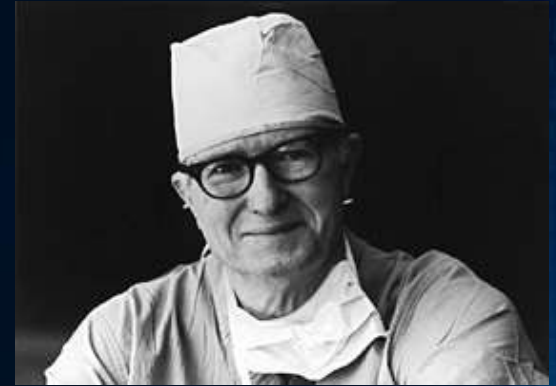
CFTR Modulation	Pre-clinical	Phase 1	Phase 2	Phase 3	To Patients
Kalydeco™ (also known as ivacaftor)					
Orkambi™ (lumacaftor + ivacaftor)					
Ataluren (formerly known as PTC124)					
VX-661 + ivacaftor					
Riociguat					
QBW251					
N91115					
QR-010					
Restore Airway Surface Liquid	Pre-clinical	Phase 1	Phase 2	Phase 3	To Patients
Hypertonic Saline					
Bronchitol					
P-1037					
Mucus Alteration	Pre-clinical	Phase 1	Phase 2	Phase 3	To Patients
Pulmozyme®					
Anti-Inflammatory	Pre-clinical	Phase 1	Phase 2	Phase 3	To Patients
Ibuprofen					
Alpha 1 Anti-Trypsin					
CTX-4430					
JBT-101					
Anti-Infective	Pre-clinical	Phase 1	Phase 2	Phase 3	To Patients
Inhaled Tobramycin					
Azithromycin					
Cayston®					
TIP (TOBI Inhaled Powder)					
Levofloxacin (Inhaled)					

Lung Transplantation:

- However... as CF treatments and survival evolve, lung transplantation is still the last therapeutic option for end-stage lung disease.

History of Lung Transplantation

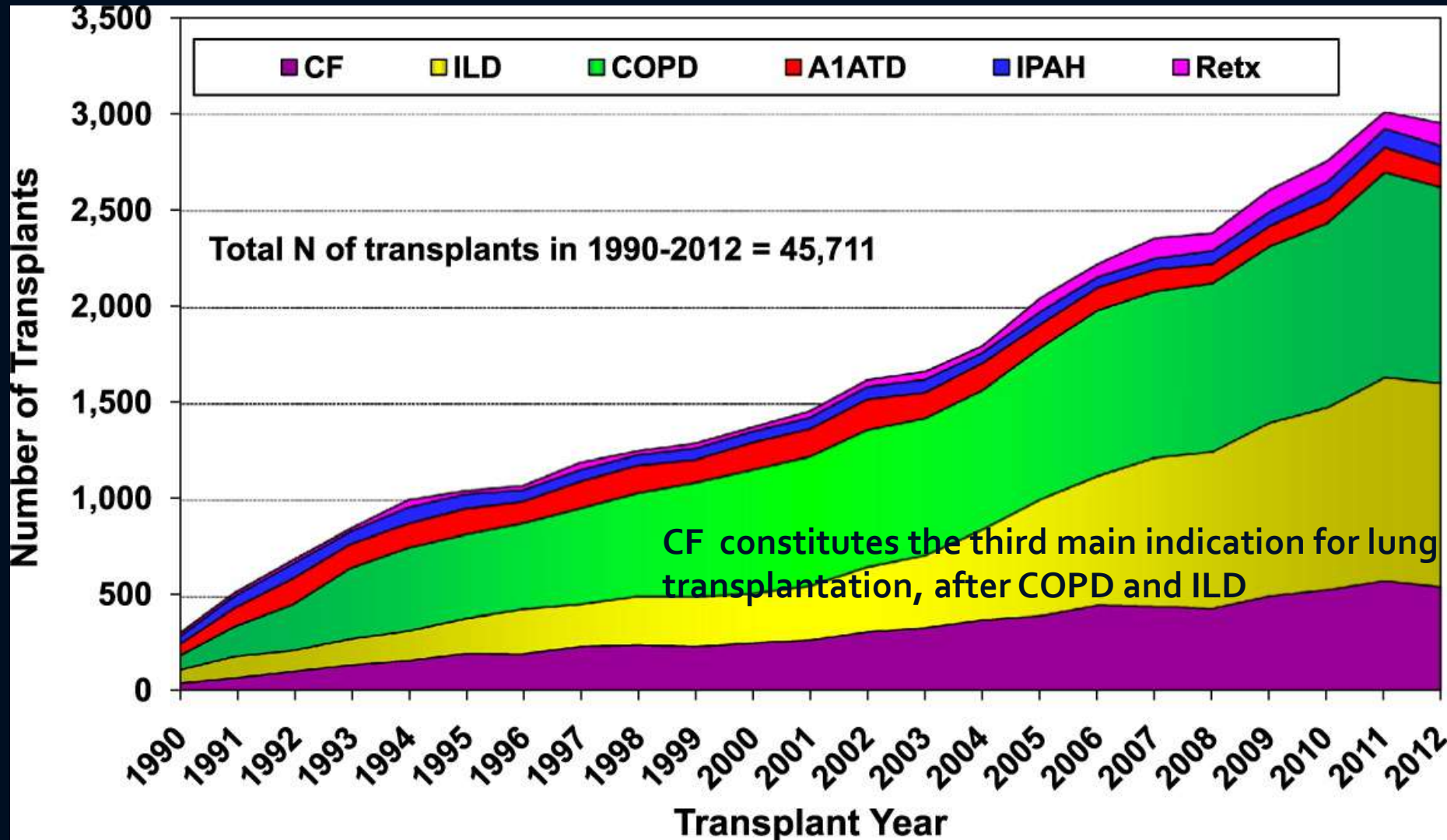
- 1963: 1st human lung transplantation (Hardy)
- 1981: heart-lung (Shumway, Stanford)
- 1983: single lung (Cooper, Toronto)
- 1986: double lung (Cooper, Toronto)
- 1988: 1st heart-lung transplantation for CF (Wallwork, Cambridge)



J.D. Hardy, MD. 1918-2003

Successful lung transplantations opened an opportunity for more than 2500 CF patients being transplanted worldwide per year

Adult lung transplantation according to indication and year of transplantation (transplants: 1990 to 2012).



Local history in Israel



- 1992: First single lung transplantation in Israel
- 1996: First lung transplantation in CF in Israel
- TODAY: Rabin Medical Center - the national center for lung transplantation and follow-up in Israel With 568 lung transplants



**First Successful Heart-Lung Transplantation for Cystic Fibrosis
in Israel**

Aravot D, Kramer M, et al.

Transplantation Proceedings, 31:1875 (1999)

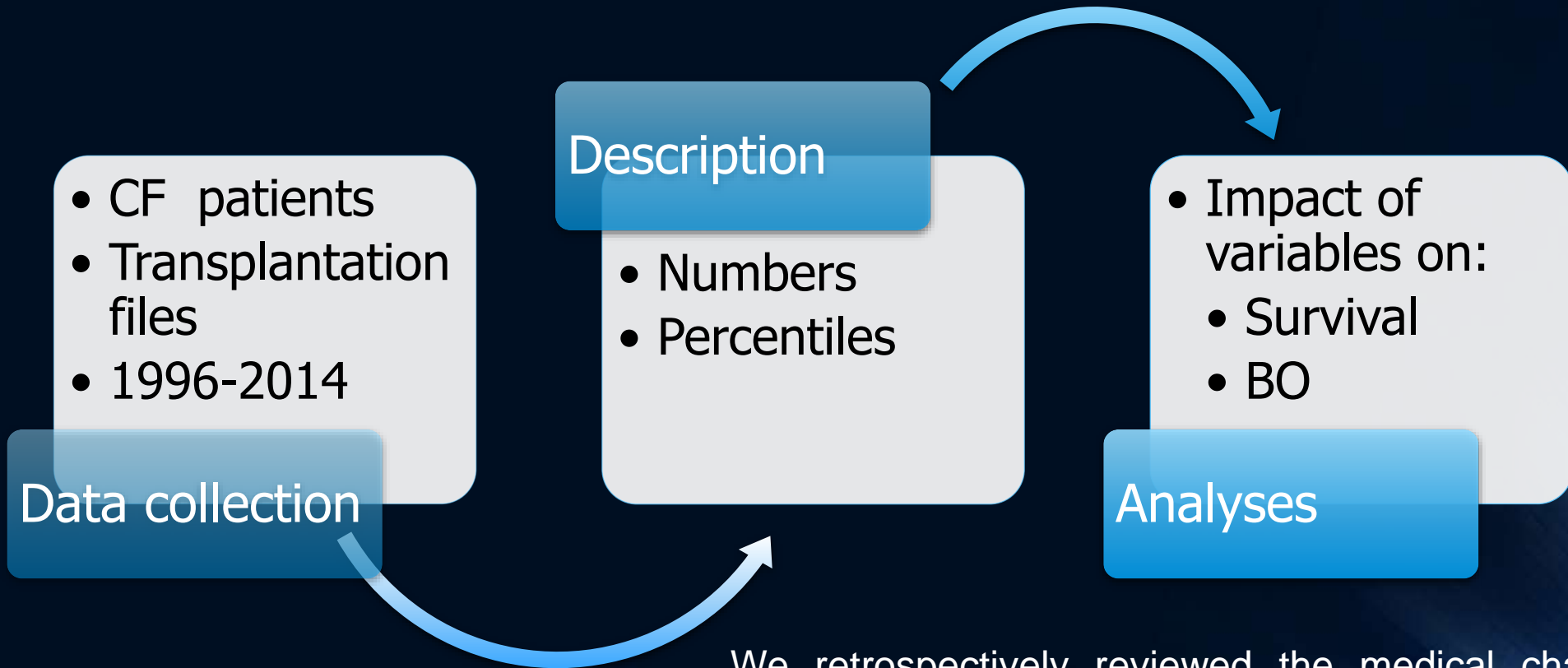


The Israeli experience and the characteristics for success

1996-2014

We aimed to evaluate the Israeli national experience with lung transplantation for patients with CF at Rabin Medical Center (RMC), and to assess the characteristics of CF patients that correlate with better outcomes.

Lung transplantation in CF patients – Study Methods:



We retrospectively reviewed the medical charts of all CF patients who underwent lung transplantation between January 1996 and December 2014 at Rabin Medical Center

Referral indications for transplantation:

- As a rule, all recipients were selected according to the International Society for Heart and Lung Transplantation (ISHLT) guidelines:
 - $FEV_1\% < 30\%$ or a rapid lung function decline (particularly in a female patient)
 - 6-minute walk distance of <400 m
 - Pulmonary hypertension
 - Clinical decline with:
 - Acute respiratory failure requiring non- invasive ventilation
 - Increasing antibiotic resistance
 - Poor recovery from exacerbations
 - Worsening nutritional status
 - Pneumothorax
 - Life-threatening hemoptysis despite bronchial embolization

When the life expectancy for the next 2 years is less than 50%

Results: Demographics

Total:

- Patients - 50
- Transplantations - 54
 - Second transplantation - 3
 - Third transplantation - 1

Age: Mean age: 28.3 ± 9.1 years (range 11-50)

Gender:

- Males - 24 (48%)
- Females - 26 (52%)

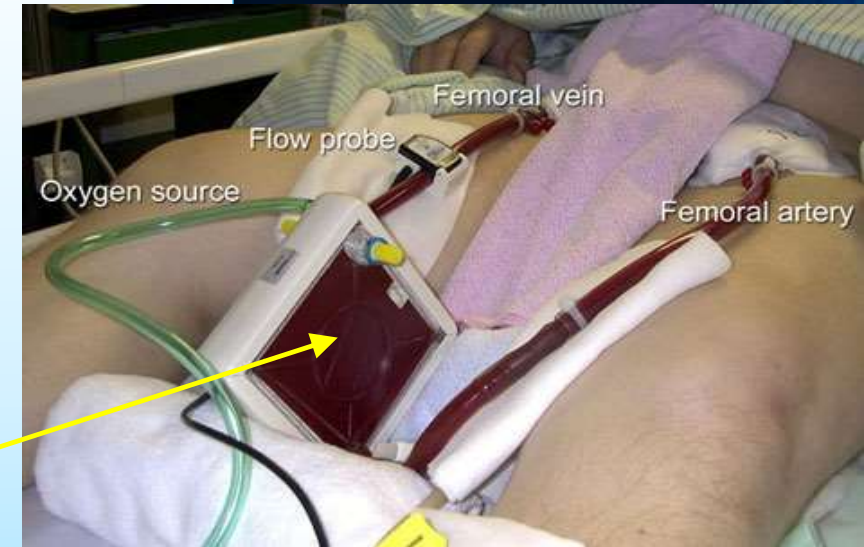
Ethnicity:

- Jews - 42 (84%)
- Arabs - 8 (16%)

Respiratory Characteristics...

• O ₂ dependence	45 (90%)
• Bipap	34 (68%)
• Tracheostomy	2 (4%)
• Mechanical (Invasive) ventilation	3 (6%)
• • Novalung*	1 (2%)
• Mean O ₂ SAT	89.2% \pm 3.9
• Mean PCO ₂	57.3 \pm 9.7 mmHg

* Novalung = Artificial Lung Device, a bridge to transplantation

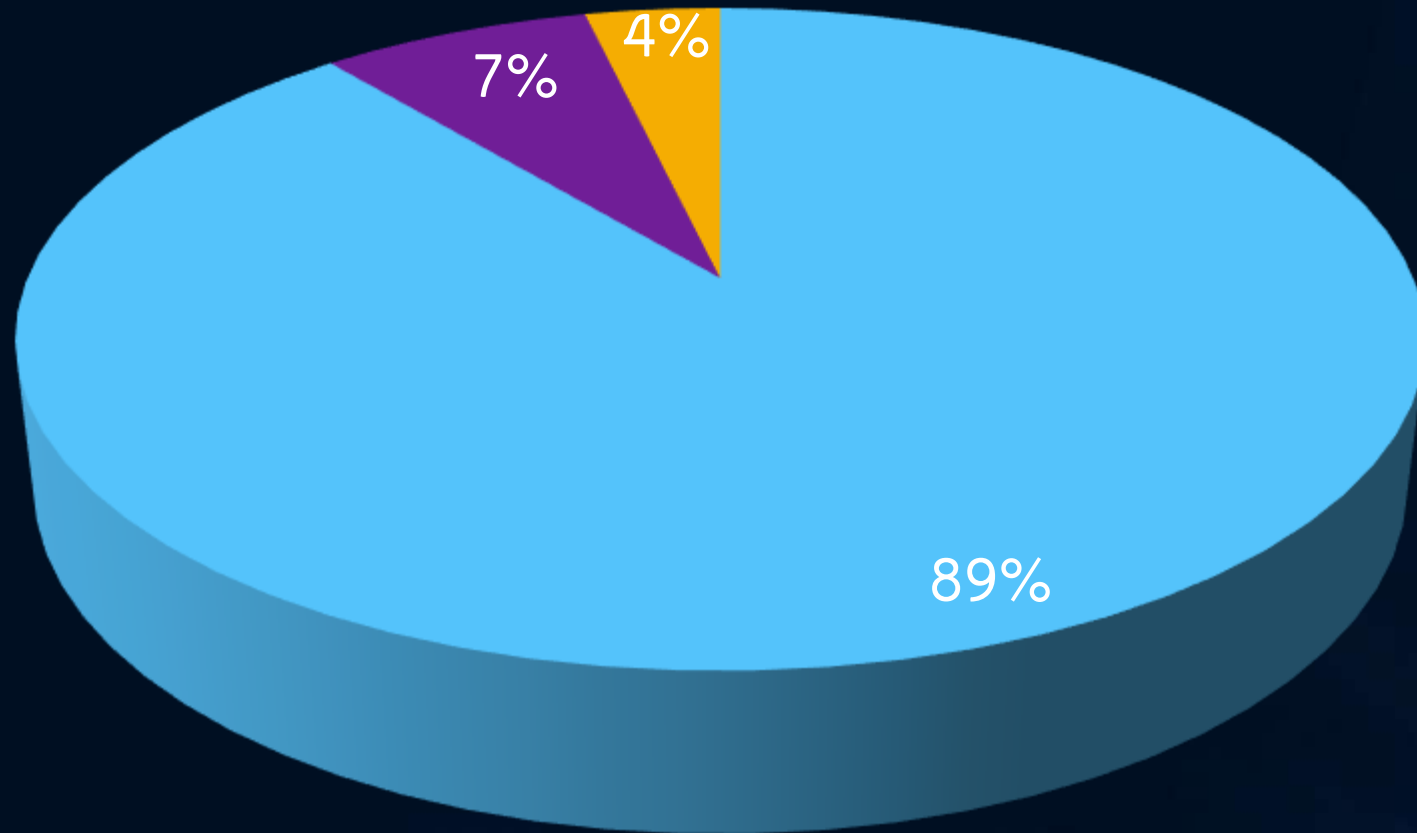


CF patients characteristics

• Pancreatic insufficiency	46 (92%)
• CF Related Diabetes	36 (72%)
• Mean HBA1C	$7.17 \pm 2.7\%$
• Liver disease	8 (16%)
• Gastrostomy	18 (36%)
• Mean BMI	$17.8 \pm 3.4 \text{ kg/m}^2$
• Mean Weight	$48.7 \pm 9.6 \text{ kg}$
• Mean Height	$162.6 \pm 10.4 \text{ cm}$

Type of transplantation

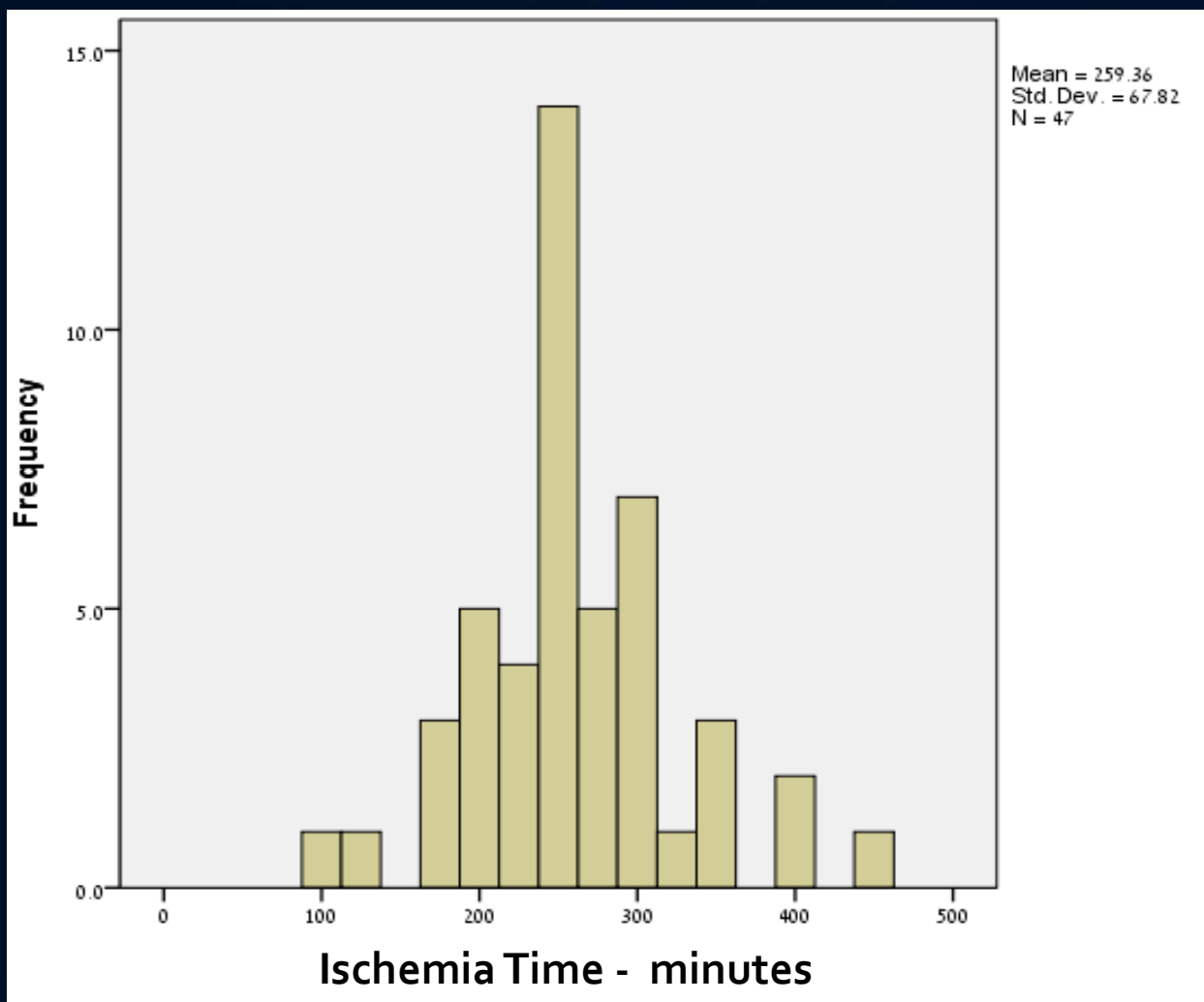
■ 2 lungs ■ heart and 2 lungs ■ 1 lung * d/t previous pneumonectomy



N=54 transplantations

Operative & Perioperative data:

Ischemia time graph



Mean Ischemia time 259 ± 67 min
(~4 hours) for the 2nd lung

Cold Ischemia Times

Organ	Accepted CIT Hours
Heart	3-4
Lung	3-5
Liver	<24
Kidney (CS)	24-36
Kidney (MP)	72
Pancreas	12-24
Intestine	6

Operative & Perioperative data:

- ECMO during operation 17 (31%)
- Mean ICU LOS 12 \pm 22 days
- Mean Department LOS 16.3 \pm 23 days

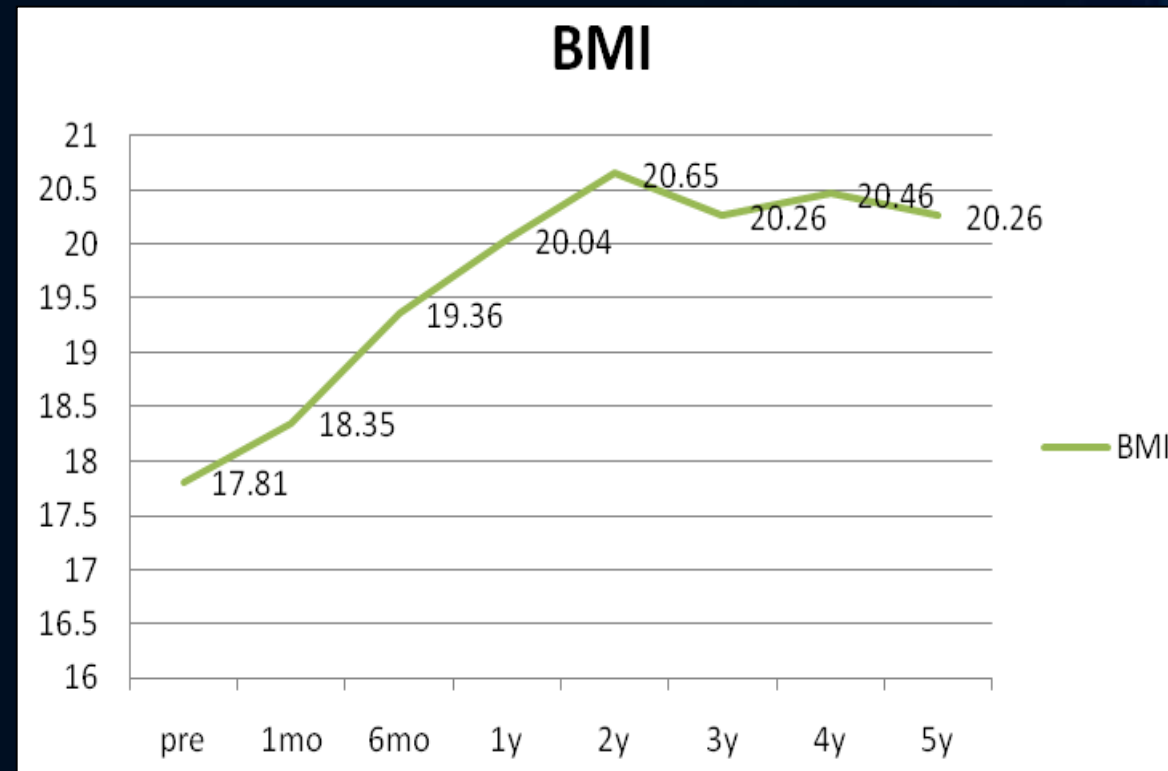
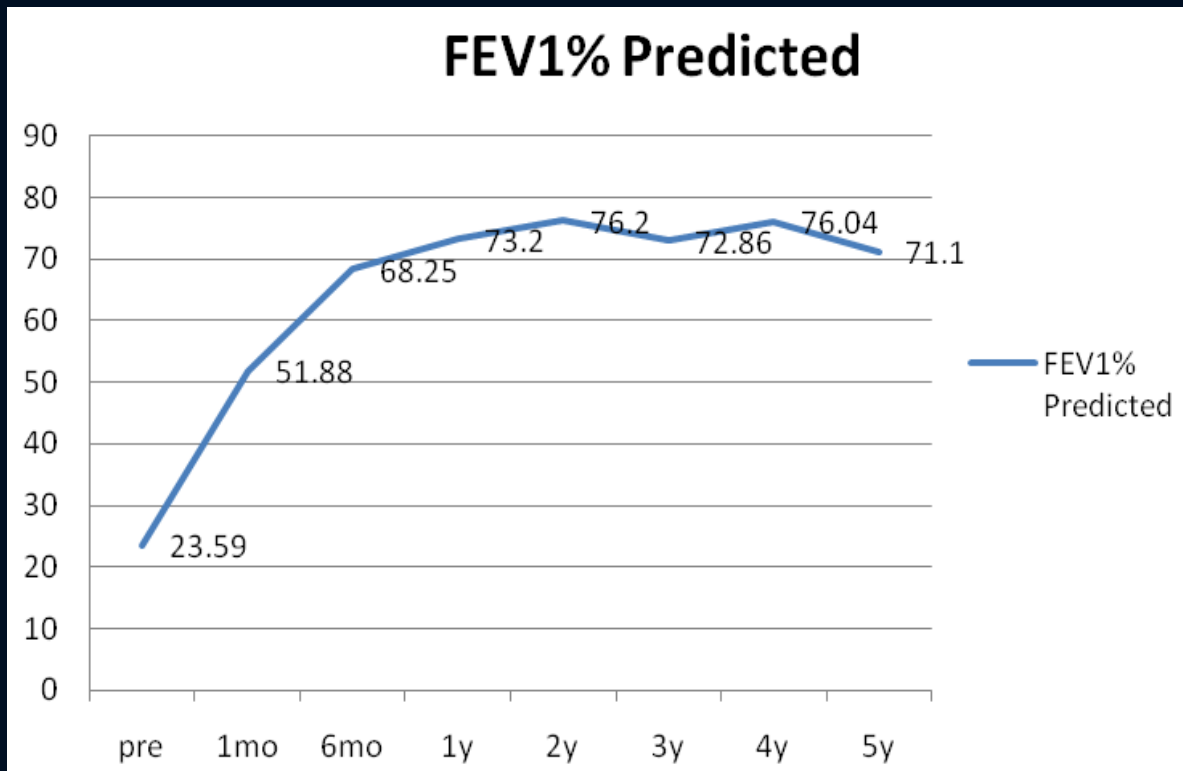
ECMO = Extracorporeal Membrane Oxygenation

ICU = Intensive Care Unit

LOS = Length of stay

Transplantation results...

Post-Operative Change in FEV1% and BMI (Means)



Pulmonary function improved from FEV₁% predicted of 23.6±6% preoperatively to 72.45±19.4%, 1 year post transplantation. There is a parallel increase in FEV₁ and BMI till they get to a plateau after 1 year

Survival:

For the whole group actuarial survival rates are:

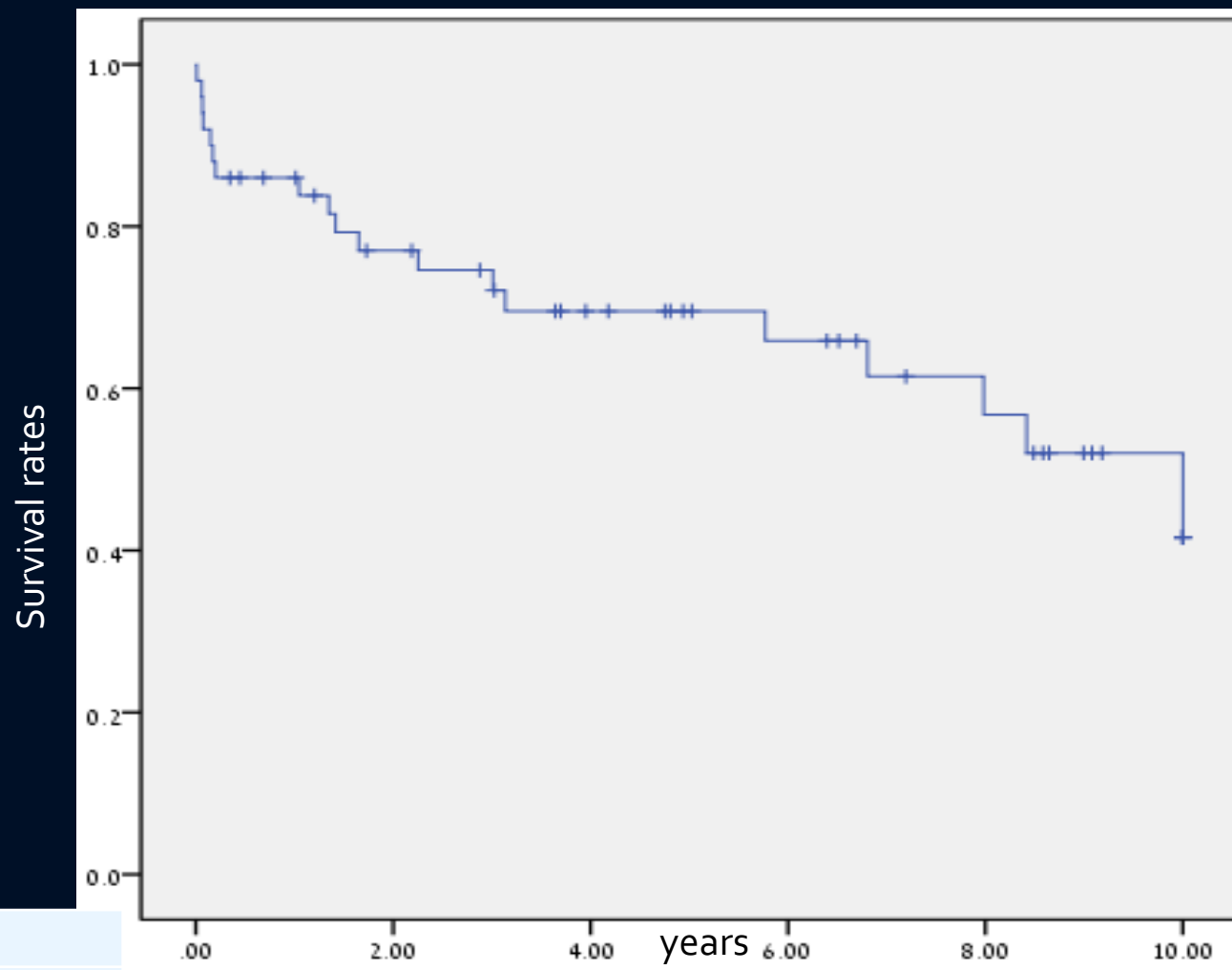
83% for 1 year

68% for 3 years

62% for 5 years

and 39% for 10 years

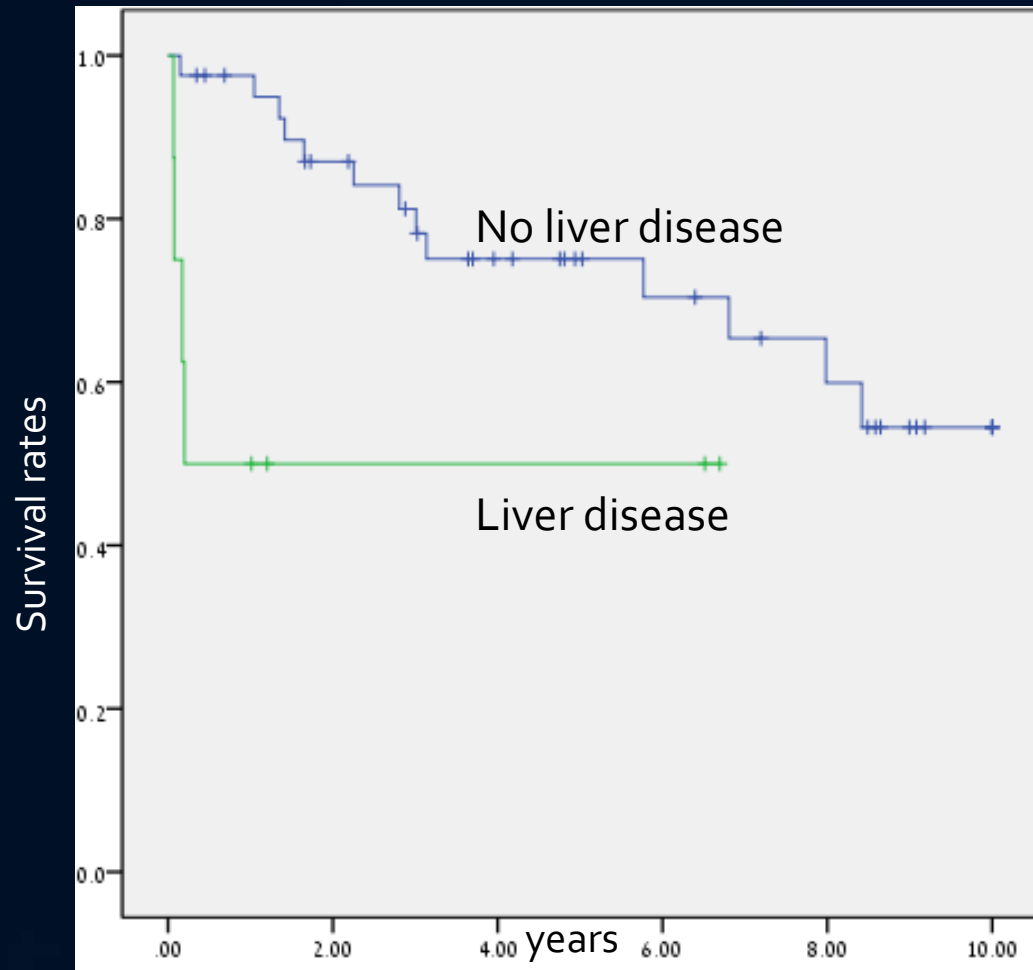
Kaplan-Meier survival curve



Mean				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
6.835	618.	5.623	8.048	10.000	1.583	6.898	13.102

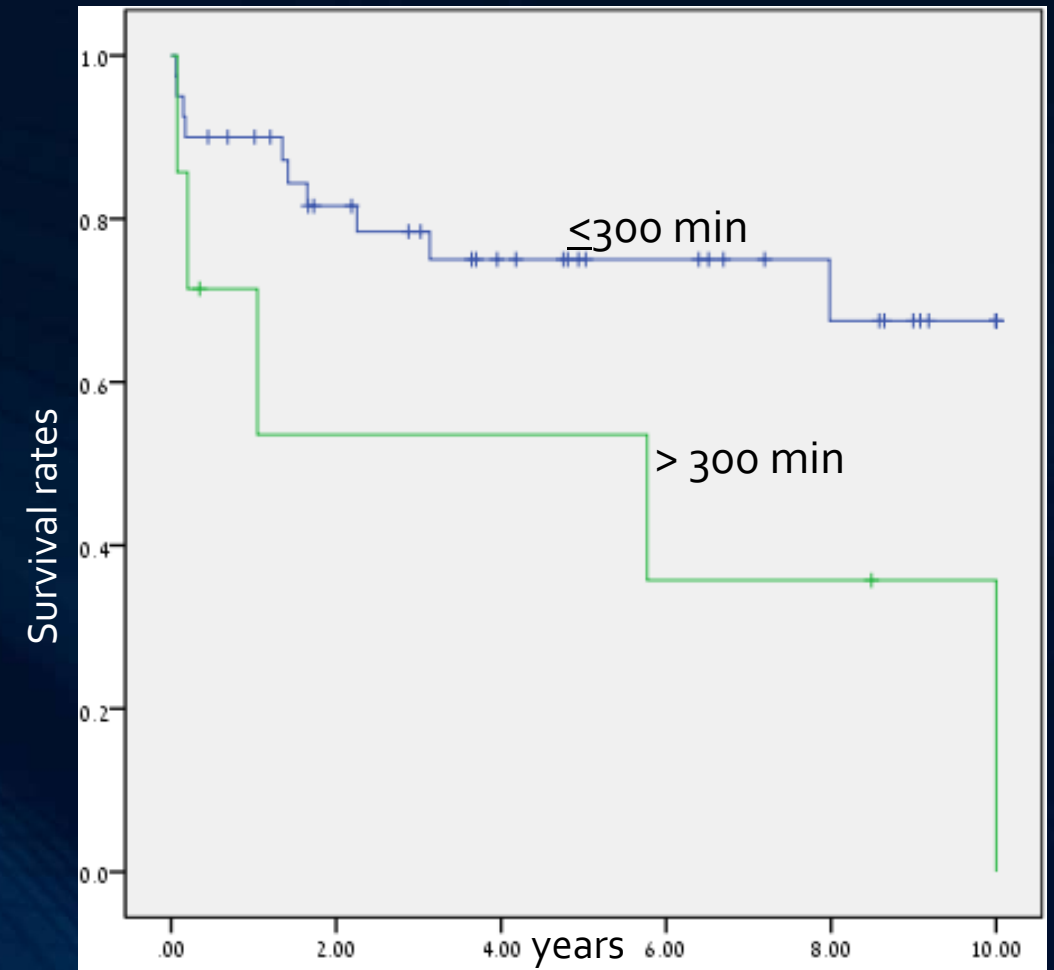
Variables correlated with better survival:

I. No Liver Disease



p value = 0.012

II. Less Ischemia time

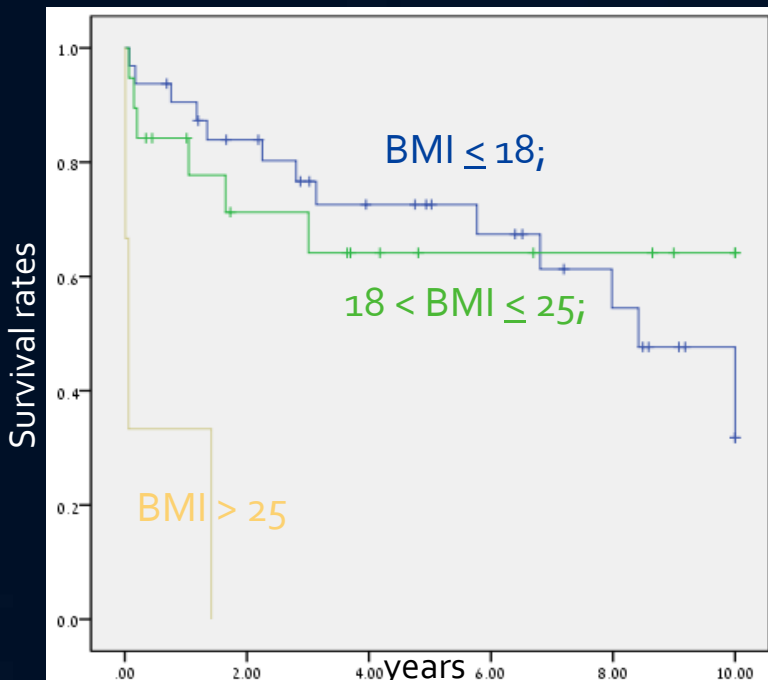


p value = 0.023

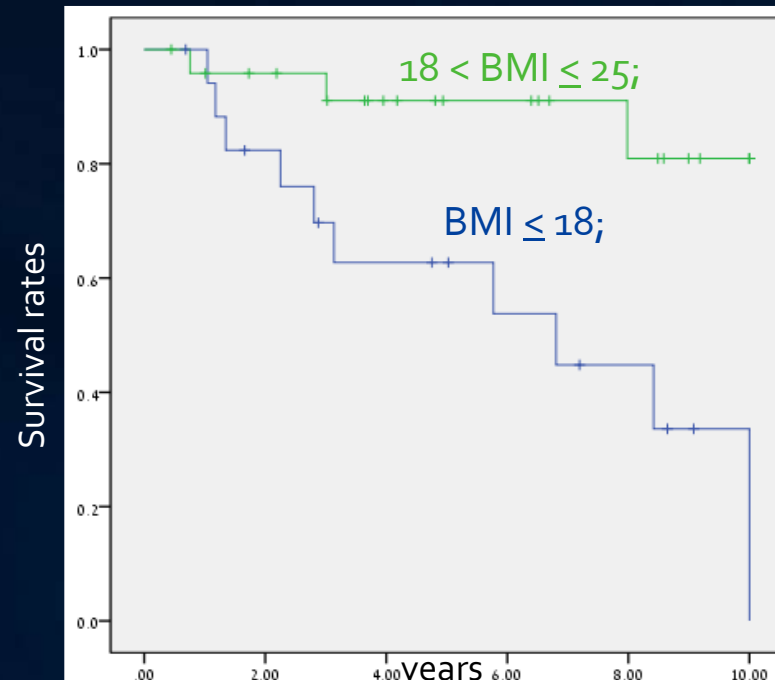
III. BMI correlated with better survival:

Kaplan-Meier survival curves stratified by BMI

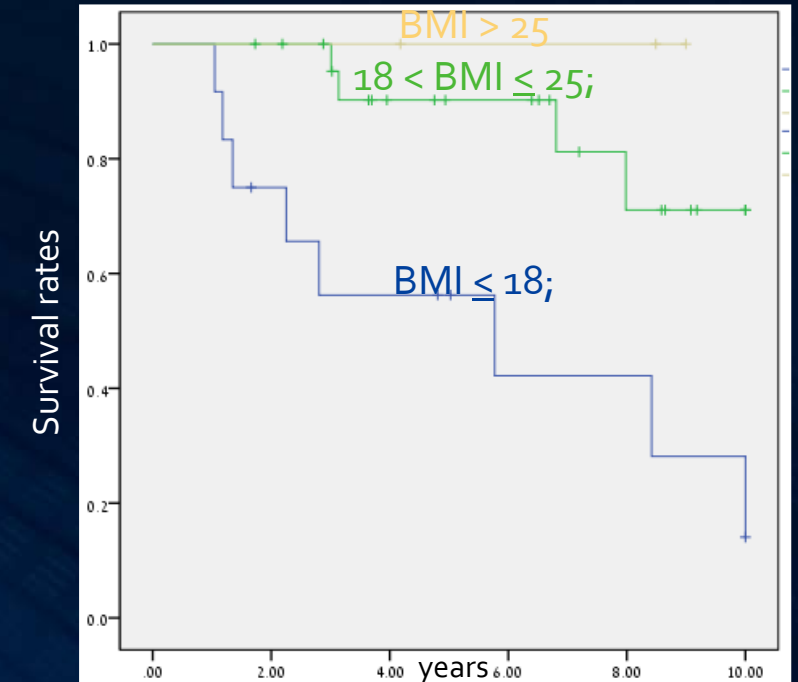
pre-transplantation 6 month post trans. 1 year post trans.



p value < 0.001



p value = 0.002

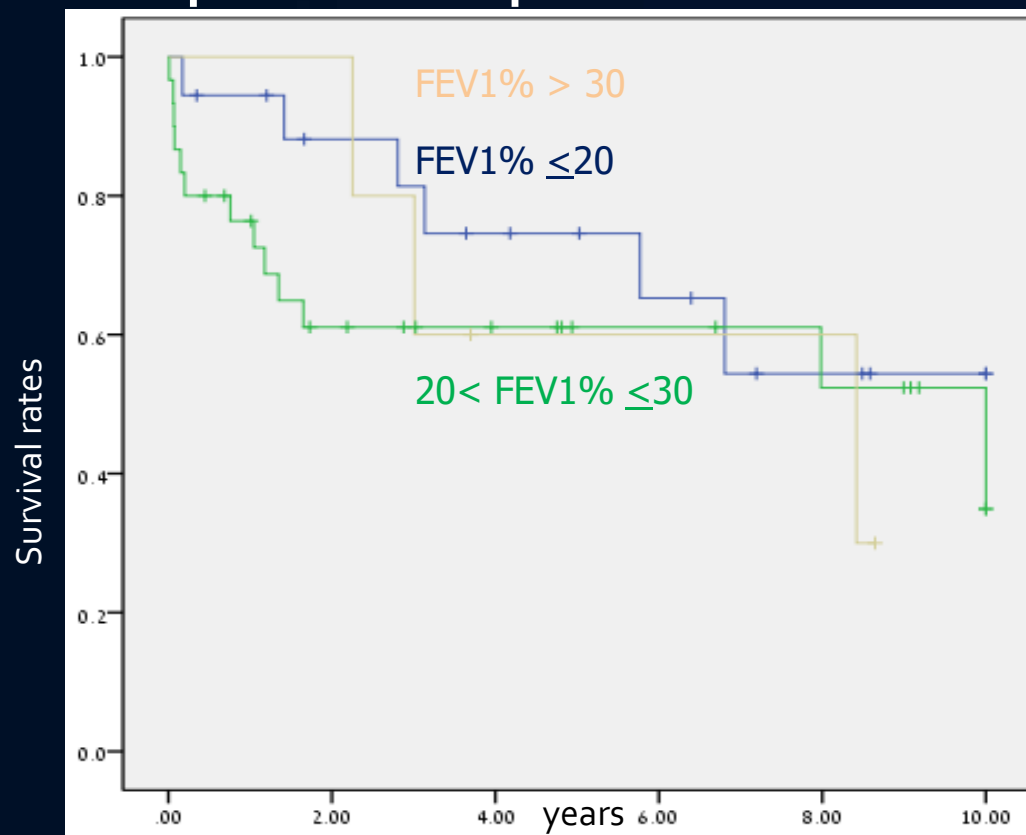


p value = 0.003

In a multi-variant analysis, using Cox regression, we found that BMI 1 year post transplantation is the sole determinant and the most influencing variable on survival.

IV. FEV1% 6 months post trans. correlated with survival:

pre-transplantation



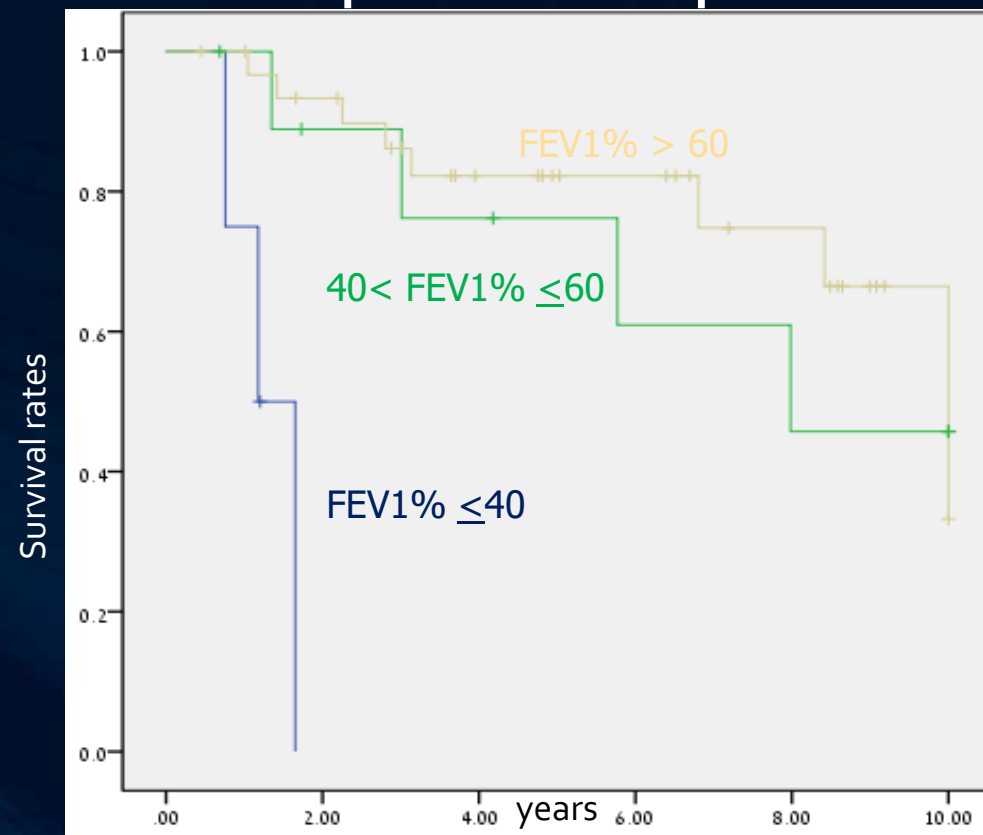
1 Blue line = FEV1% ≤ 20

p value = NS 0.5

2 Green Line = 20 < FEV1% ≤ 30

3 Brown line = FEV1% > 30

6 month post transplantation



1 Blue line = FEV1% ≤ 40

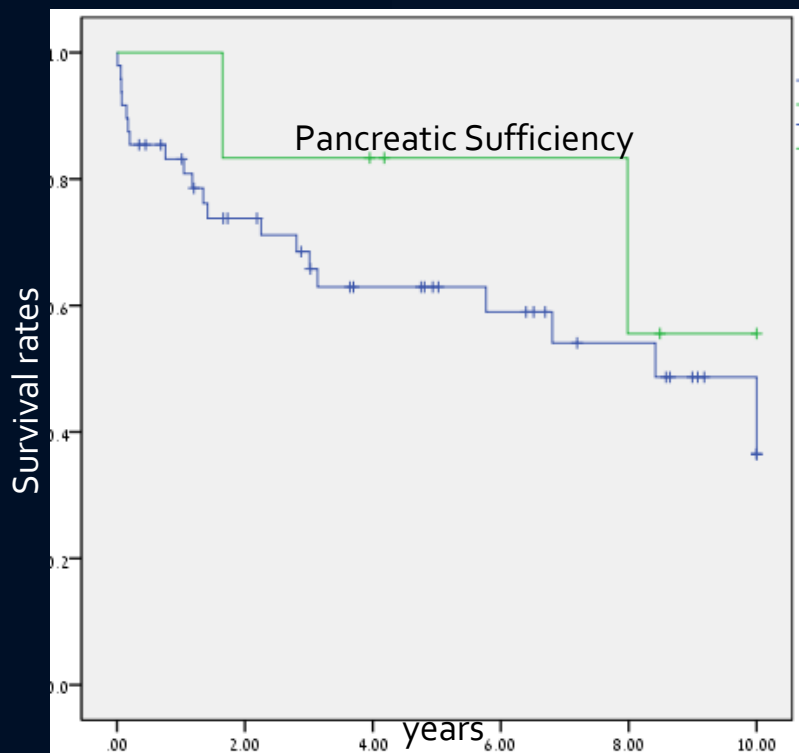
p value < 0.001

2 Green Line = 40 < FEV1% ≤ 60

3 Brown line = FEV1% > 60

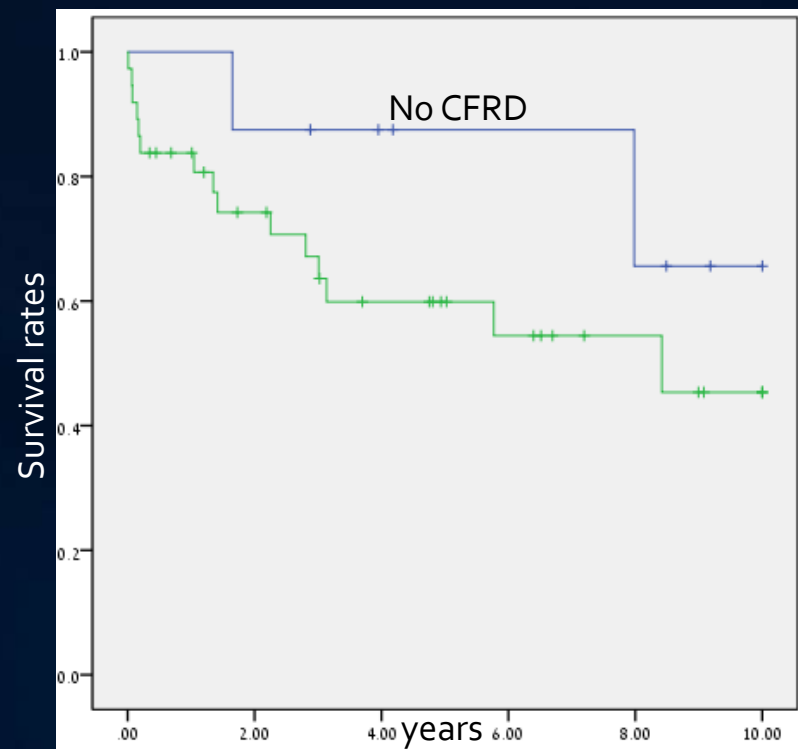
No correlation with better/worse survival

Pancreatic sufficiency



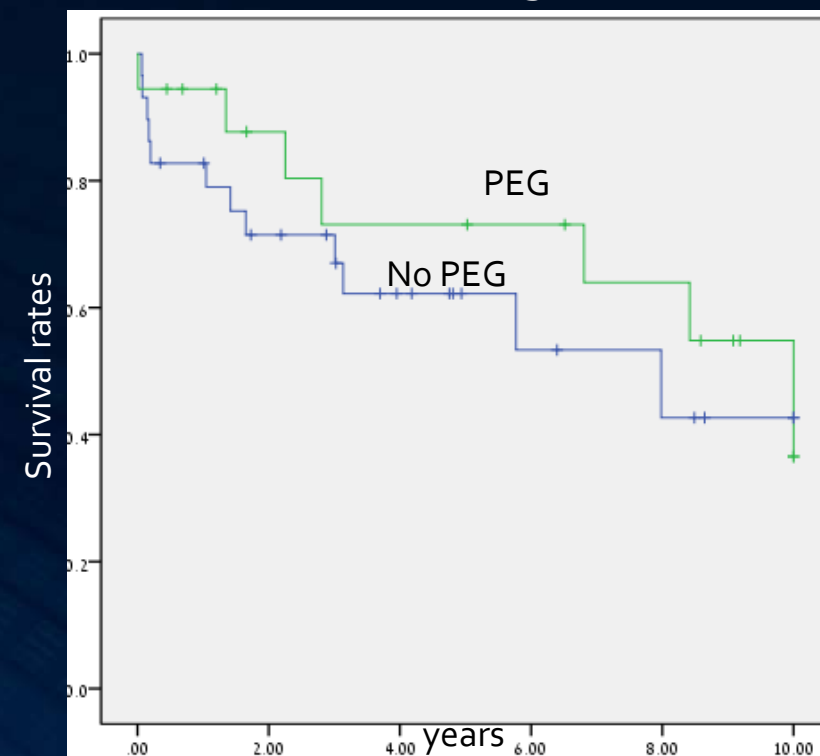
P value = NS m/p d/t small numbers of PS

CF Related Diabetes



P value = NS 0.2 m/p d/t small numbers of non CFRD

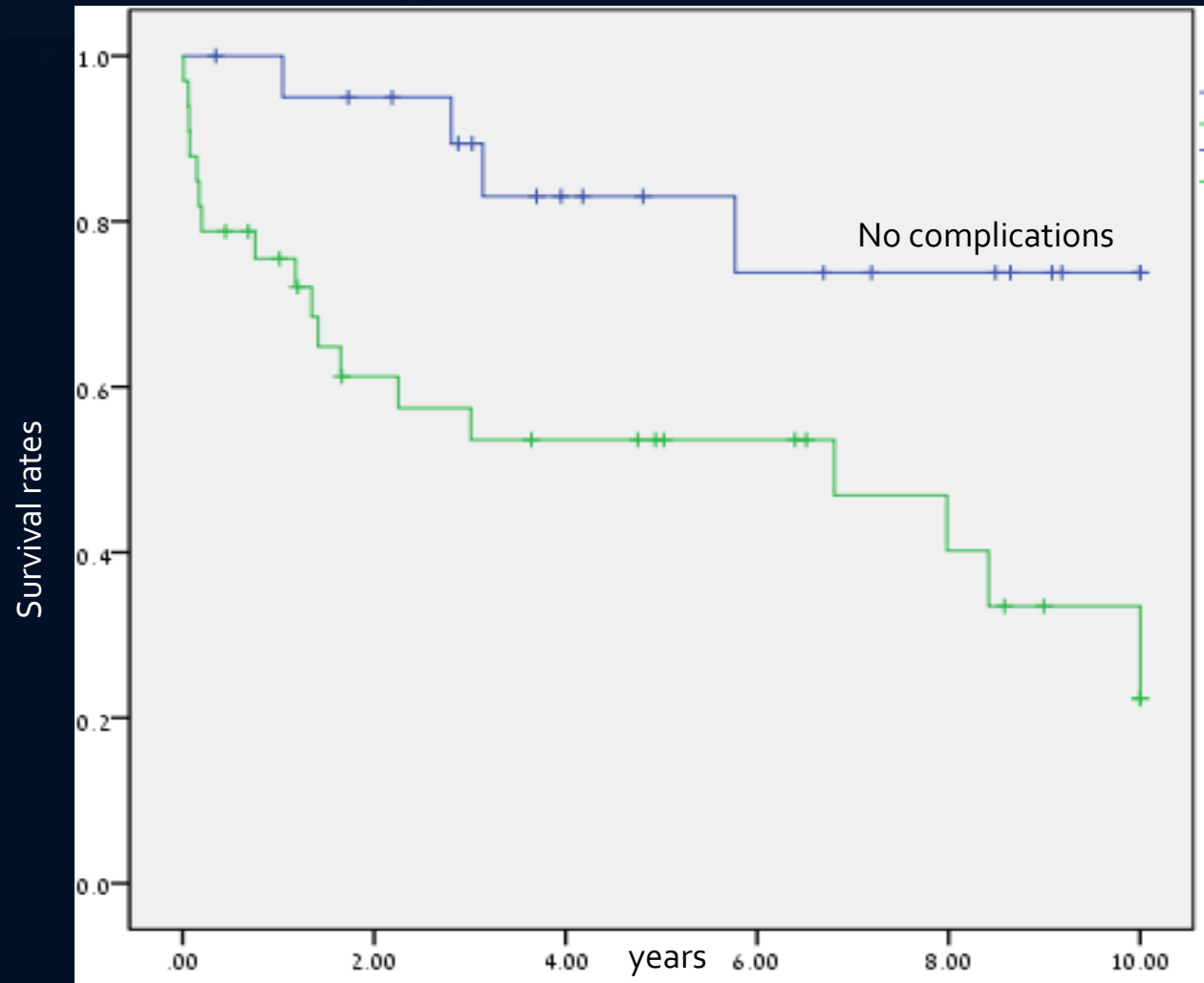
PEG usage



P value = NS 0.48

Also: Gender, age, type of transplantation, oxygen dependency, BIPAP usage, O₂ saturation, ECMO during surgery, stent insertion.

Perioperative complications: Always better without



p value = 0.008

Complications: Early/Peri-Operative

- Total N=47
 - No complications (45%)
 - Yes complication (55%)
 - Type
 - Acute infections* 12 (25%)
 - Pneumothorax/Pleural Effusion 9 (19%)
 - Vascular hemostasis** 7 (15%)
 - Pulmonary edema 6 (12%)
 - Neurology*** 6 (12%)
 - Hyperacute/Acute rejection/
Graft malfunction 4 (8%)
 - MOF/Renal/Liver failure 4 (8%)
 - Early death 6 (12%)
- *Sepsis; Pneumonia; Line infection
- **Bleeding; Thrombosis; Vascular stenosis
- ***Stroke; Ptosis; Vocal cord paralysis

At 30 days following operation

Late complications

Total complications N=118

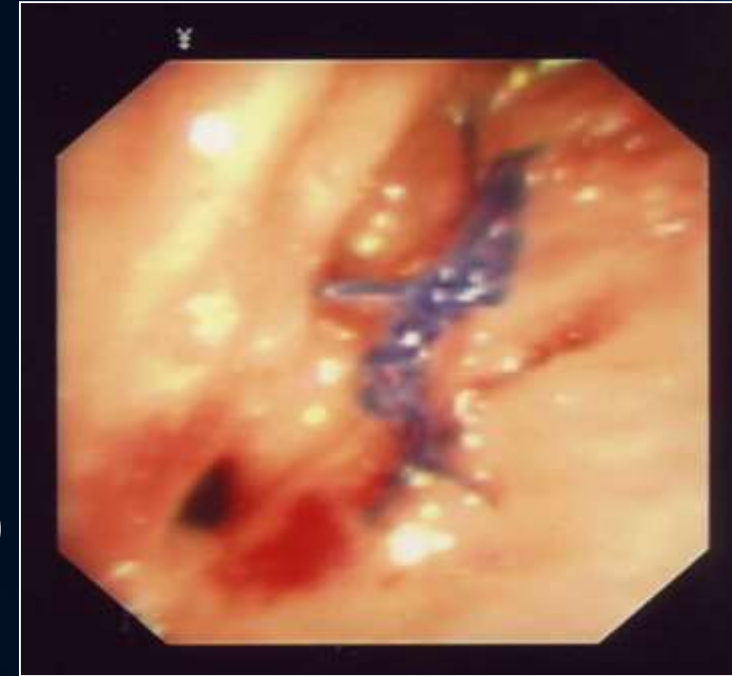
Anastomosis complications		21	17.7%
Gastrointestinal	DIOS (Distal Intestinal Obstruction Syndrome)	7	5.9%
	Gastroparesis, GERD, Aspirations	8	6.7%
Diaphragmatic paresis		11	9.3%
Sinusitis		10	8.4%
Neurology complications		9	7.6%
Lung Infections	Pneumonia/Necrotizing pneumonia	8	6.7%
Nephrology complications	Renal failure/Nephrolithiasis	8	6.7%
PTLD (Post Transp. Lymphoproliferative disease)		5	4.1%

Also : Pleural/pericardial Effusion/Pneumothorax, Hematologic comp., Sepsis, Skin Infection/Rash, Thrombosis/edema, Cholestasis/Cholecystitis/Liver enzyme elevation/Pancreatitis, Subglottic stenosis, DKA, Cataract, Arthritis/Arthralgia, MI/CHF.

Management of Complications

Anastomosis treatment	32(63%)
FESS	6 (12%)
Tracheostomy	3 (6%)
Gastrointestinal procedures (Cholecystectomy, Colonoscopy, Balloon dilatation)	3(6%)
Kidney transplantation	2 (4%)
Pericardiotomy	1 (2%)
Total treatments	N=51

FESS = Functional Endoscopic Sinus Surgery

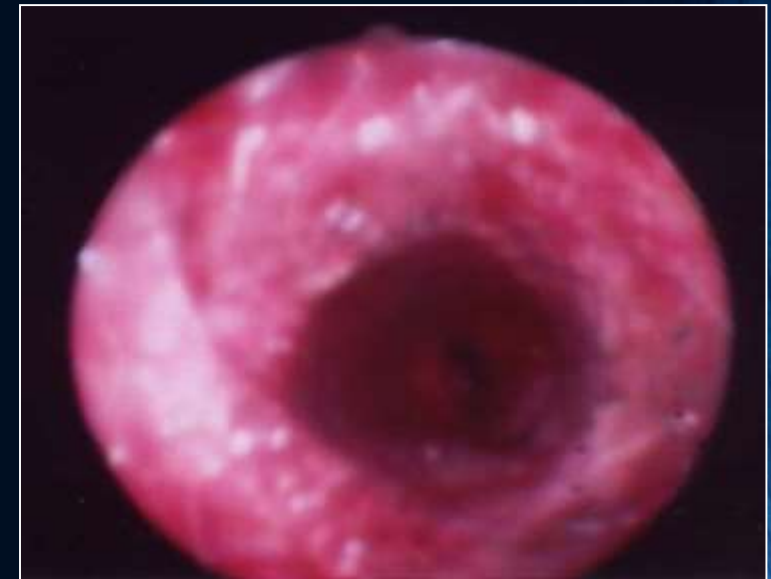


Treatments for anastomotic stenosis

• Laser bronchoscopy	9 (28%)
• Balloon dilatation	7 (21%)
• Stent insertion	6 patients (18%)
	8 stents
• Granulation/Polyp removal	2 (6%)
• Mechanical dilatation	3 (9%)
• Amplatzer device	1 (3%)
• Brachiththerapy	1 (3%)
• Cryotherapy	1 (3%)

Total treatments

N = 32



Lung infections: The bug will not disappear...

• Pre - transplantation:

- **Pseudomonas** 50 (100%)
- Aspergillus 22 (44%)
- Acinetobacter 1 (2%)
- MSSA 10 (20%) MRSA 2 (4%)
- Stenotr. 5 (10%)
- Serratia 2 (4%)
- Achromobacter 0 (0%)
- Klebsiella 1 (2%)
- NTM 7 (14%)
- Nocardia 2 (4%)
- ABPA 3 (6%)
- **Burkholderia cepacia** 0 (0%)

• Post - transplantation:

- **Pseudomonas** 50 (100%)
- Aspergillus 24 (48%)
- Acinetobacter 11 (22%)
- MSSA 14 (28%) MRSA 2 (4%)
- Stenotr. 6 (12%)
- Serratia 5 (10%)
- Achromobacter 2 (4%)
- Klebsiella 3 (6%) CRE 1(2%)
- NTM 3 (6%)
- Nocardia 1 (2%)
- ABPA 1 (2%)
- **Burkholderia cepacia** 0 (0%)

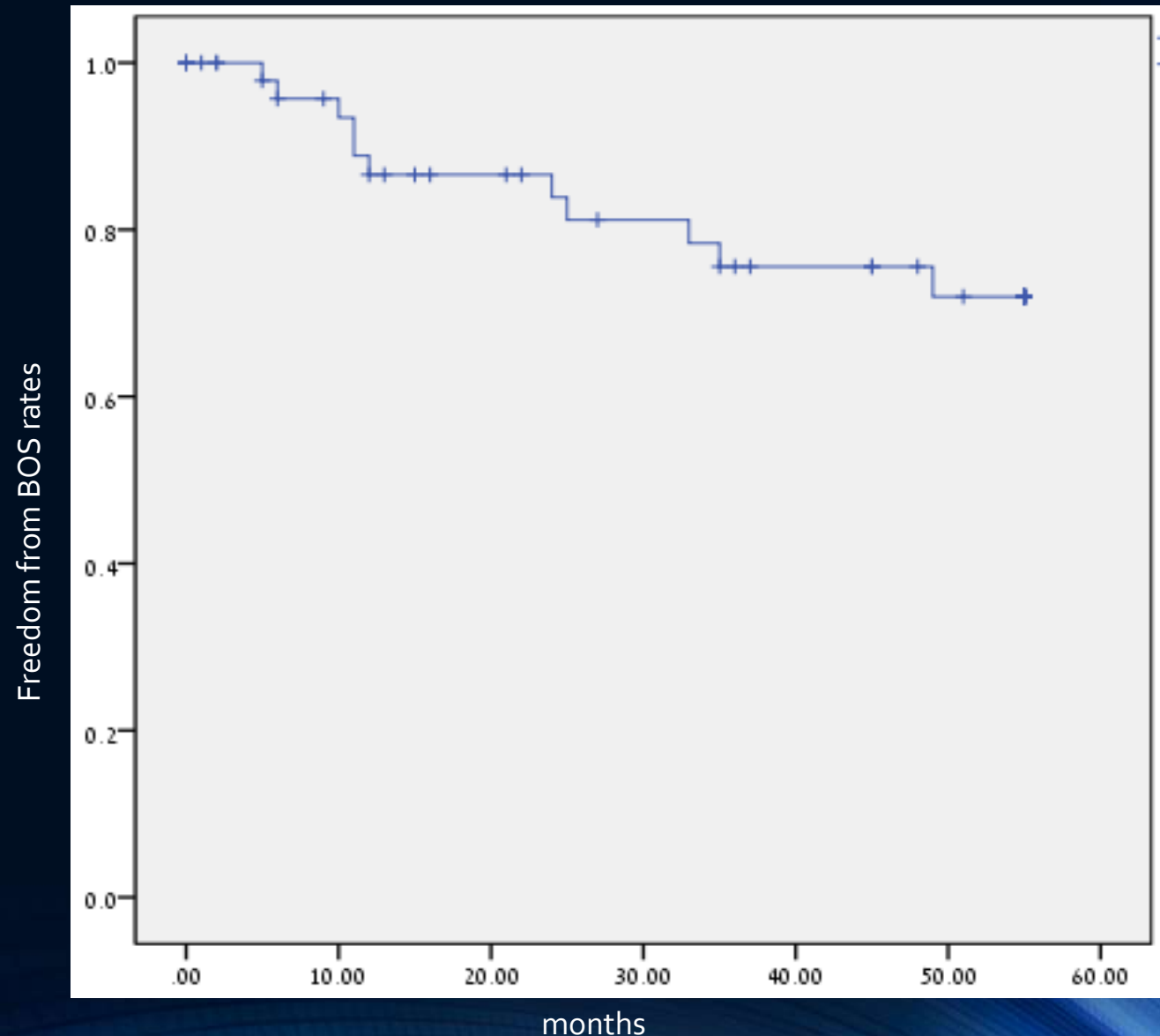


What about chronic transplant associated lung disease?

Chronic lung rejection is still the most important late complication... results in BOS or RLD

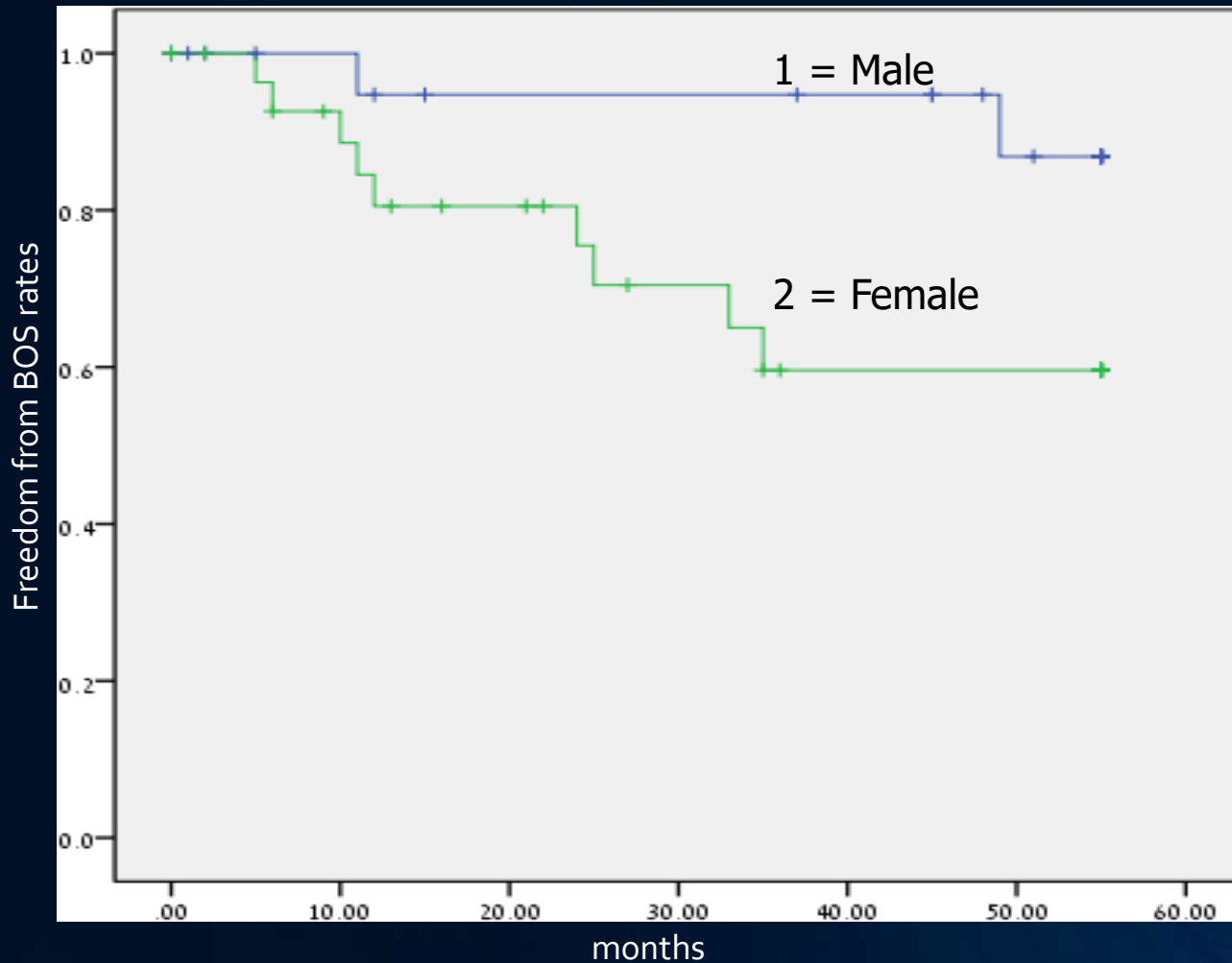
Bronchiolitis Obliterans Syndrome

- What are the variables that are related to early or late BOS?
- Definition:
 - BO1 When FEV1 decrease in 20% or more from the maximum FEV1 after transplantation



Earlier BOS correlated with:

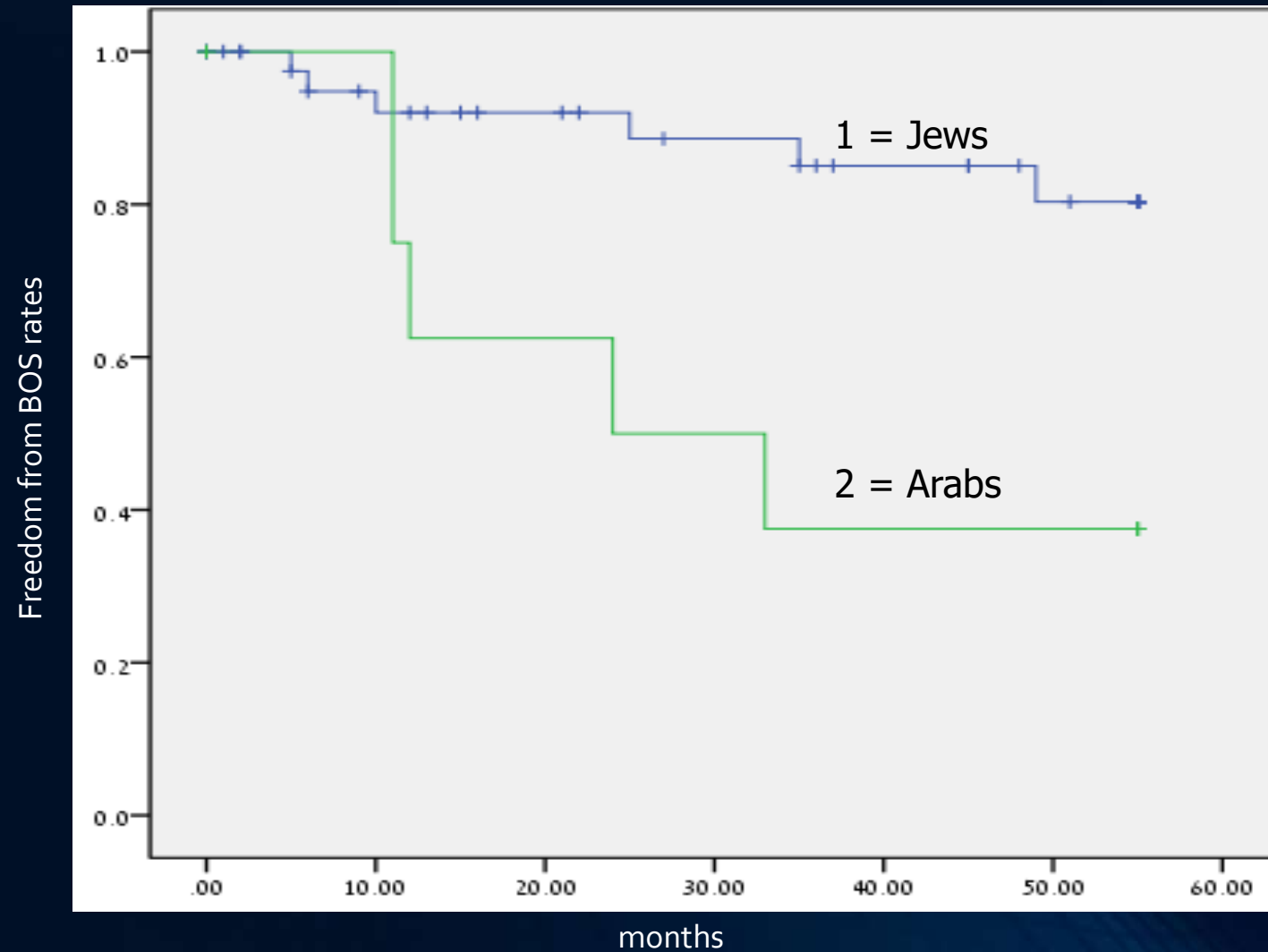
I. Gender



Males had more time of freedom from BOS

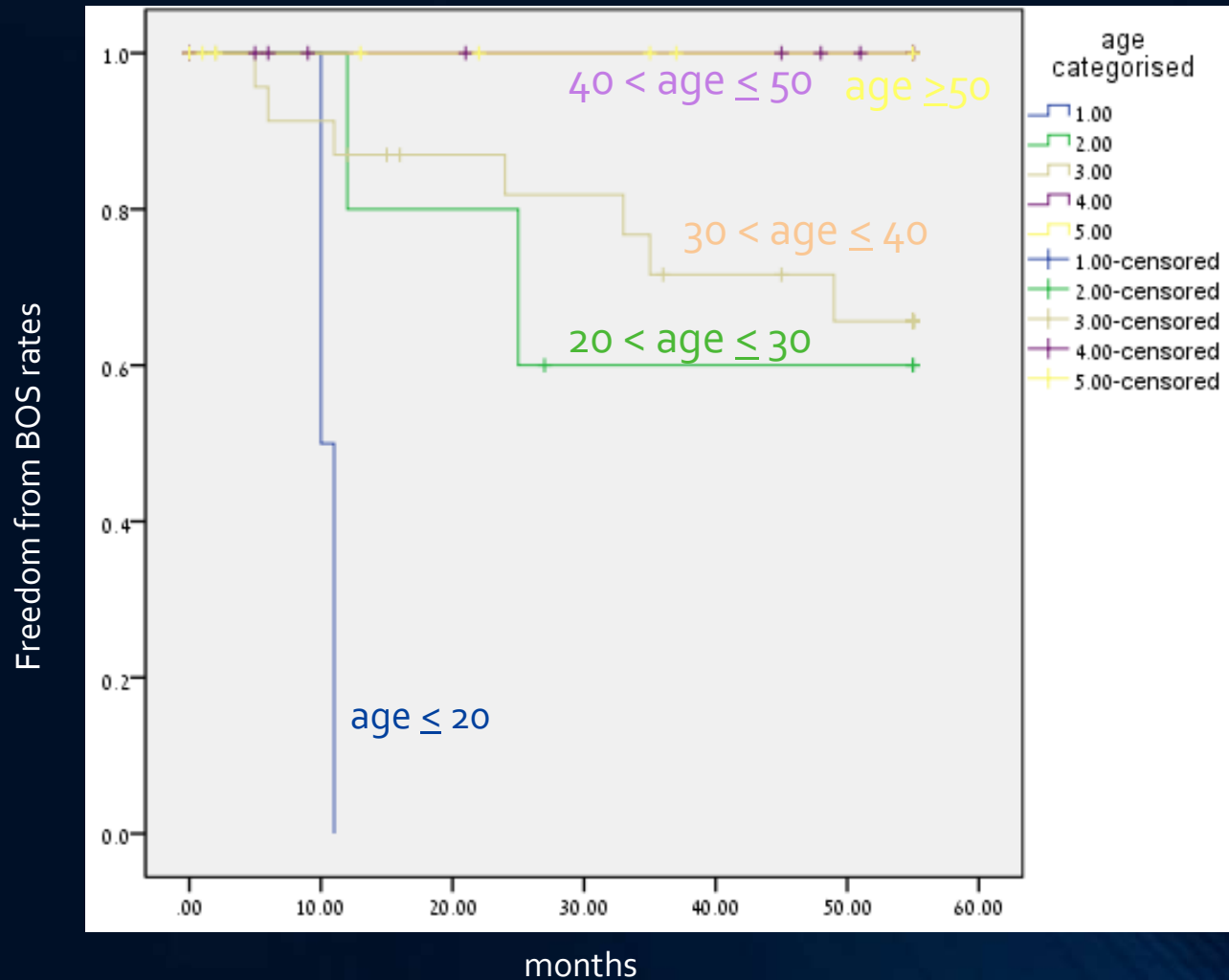
p value = 0.039

Earlier BOS correlated with: II. Arab > Jewish Ethnicity



p value = 0.007

Earlier BOS correlated with: III. Younger Age

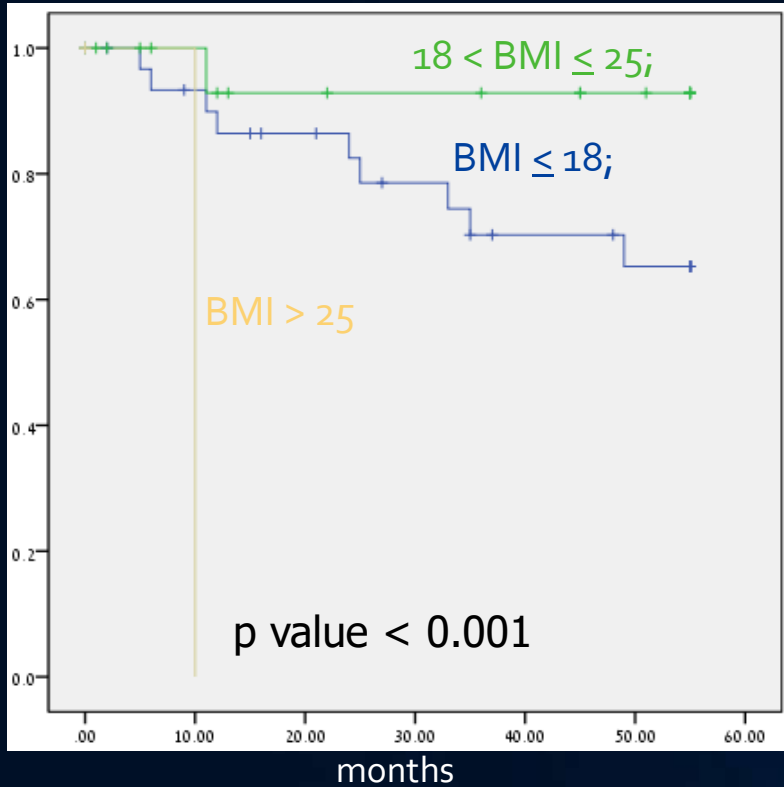


1 = age ≤ 20
2 = 20 < age ≤ 30
3 = 30 < age ≤ 40
4 = 40 < age ≤ 50
5 = age ≥ 50

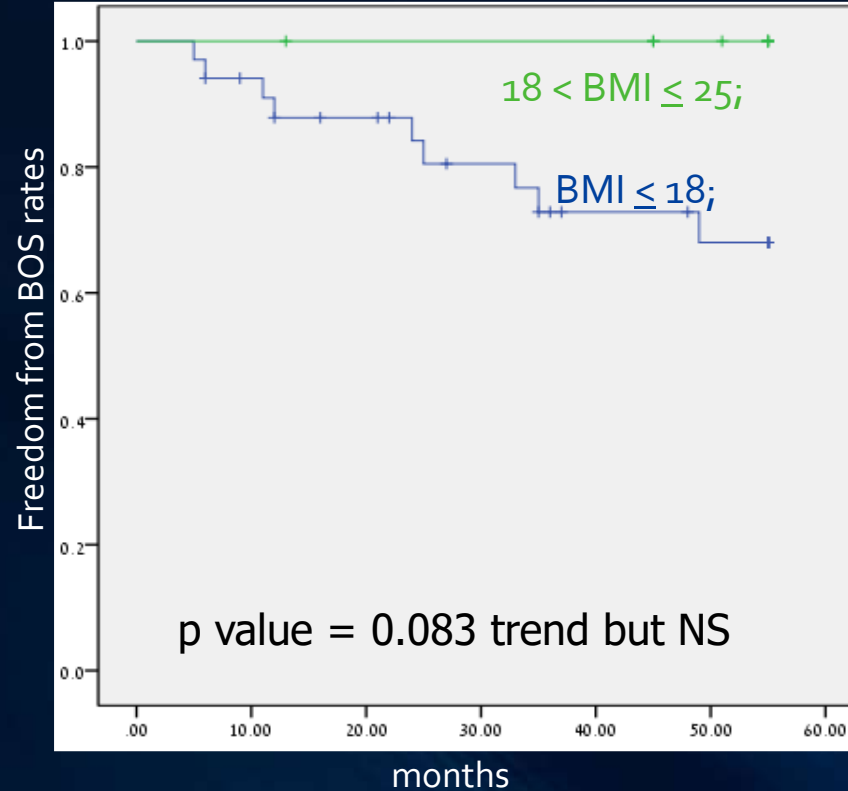
p value < 0.001

Earlier BOS correlated with: IV. BMI

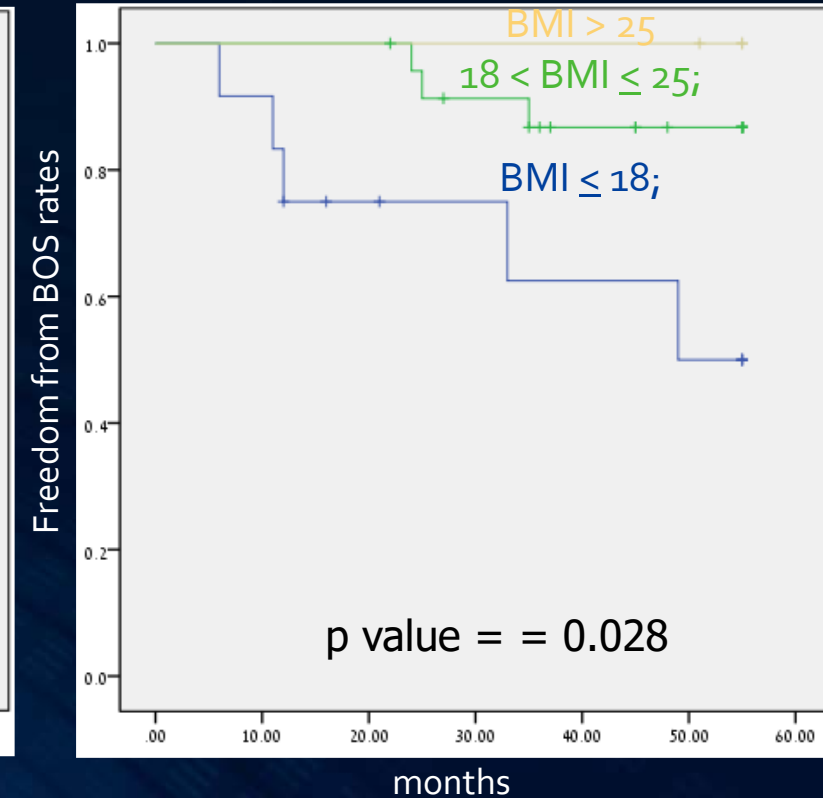
pre-transplantation



6 month post trans.

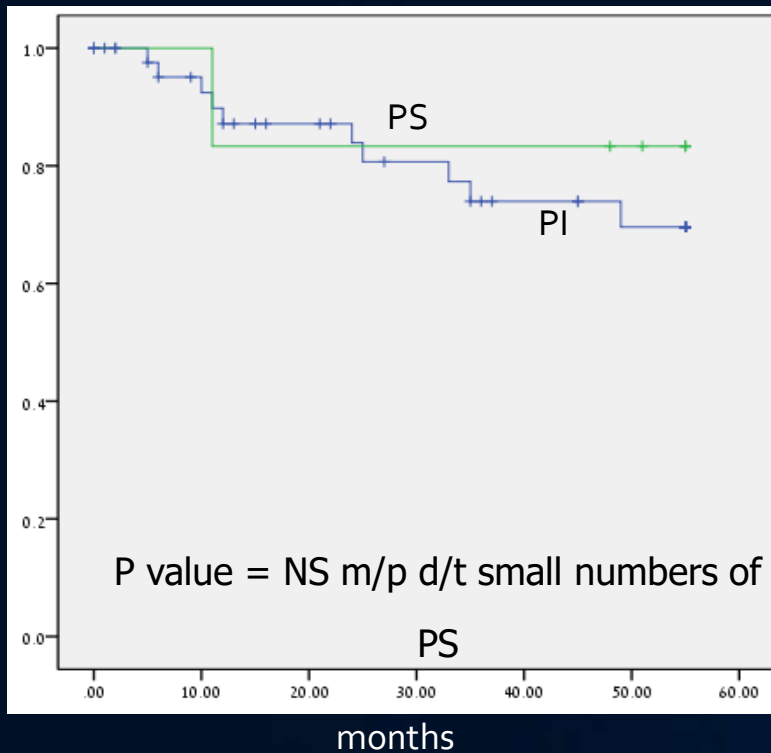


1 year post trans.

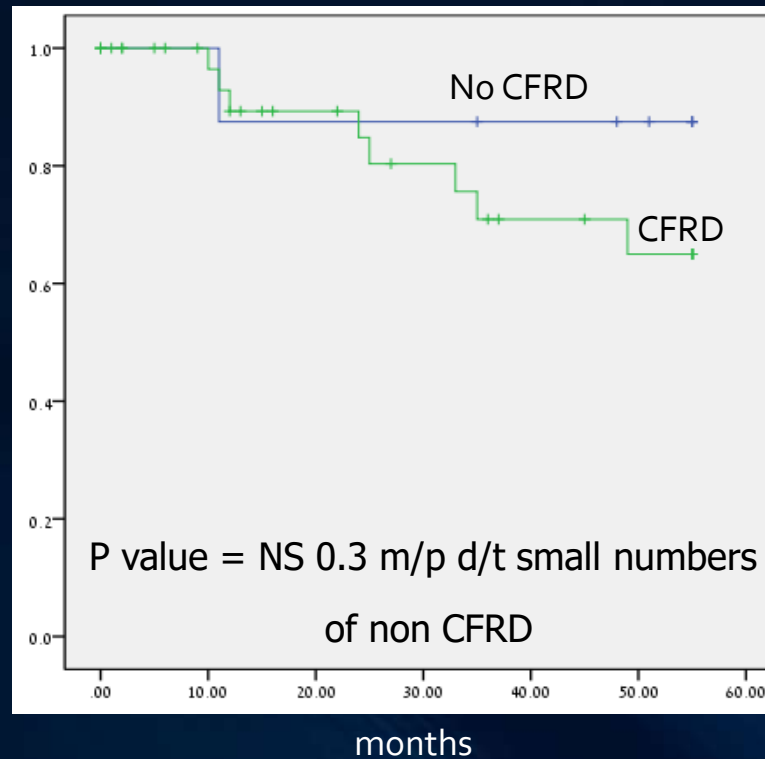


BOS was not correlated with:

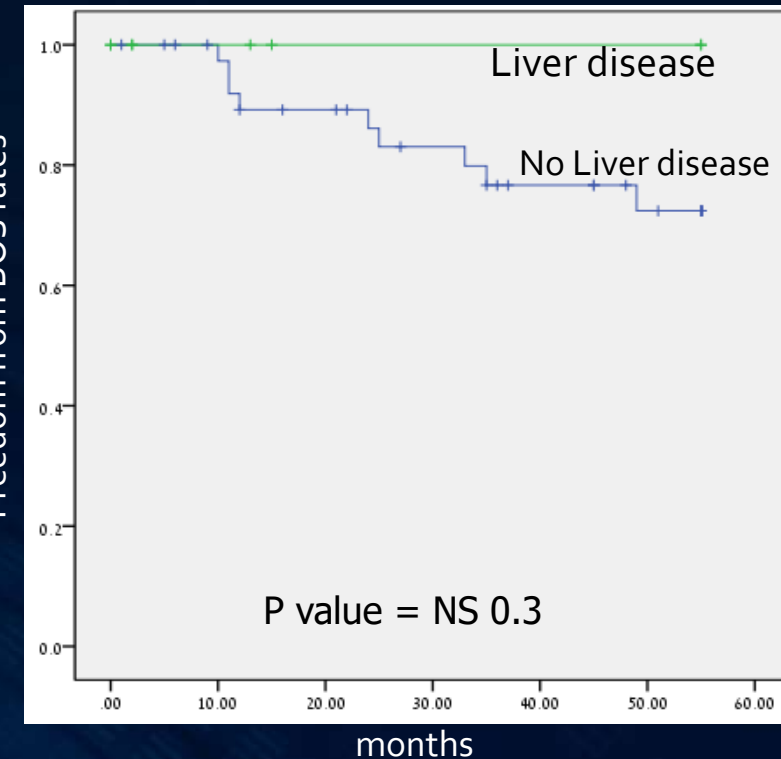
Pancreatic sufficiency



CF Related Diabetes



Liver disease



Also : Type of transplantation, oxygen dependency, BIPAP usage, O₂ saturation, gastrostomy, ECMO during surgery, stent insertion.

Discussion & Summary:

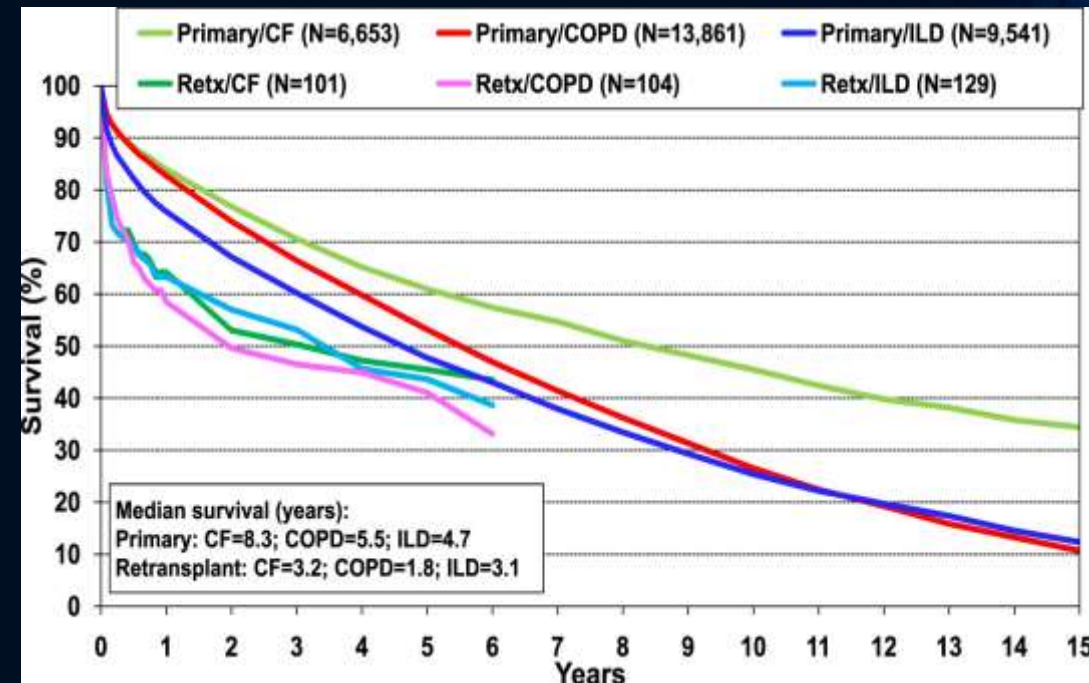
- Lung transplantation confers a survival advantage
- RMC actuarial survival rates are similar to ISHLT 2014 rates

[The Registry of the International Society for Heart and Lung transplantation (ISHLT) 2014. The Journal of Heart and Lung Transplantation, Oct 2014]

- Also similar to a large study at UK on lung transplantation among CF patients, with a 1 year survival rate of 82% and 5 year survival of 62%

[Outcomes of lung transplantation for cystic fibrosis in a large UK cohort. Thorax. Aug 2008]

Adult lung transplant recipient Kaplan–Meier survival by transplant type and diagnosis (transplants: January 1990 to June 2012)



Discussion & Summary: Nutrition

- Nutritional status after transplantation seems to be more important than the nutritional status before the transplantation.
 - Is it the weight gain that improved survival or is it the better transplantation course that improved the weight?
- Pancreatic sufficiency or insufficiency not associated with worse or better survival post-transplant.
 - This was opposite to the Canadian study who found pancreatic sufficiency to worsen survival [Stephenson AL et al. J Heart Lung Transplant. May 2015]

Discussion & Summary: “Gender Gap”

- In our study, gender was not significantly correlated with survival
 - Similar to other studies on CF transplantations
 - Different from studies on all other reasons for transplantation, in which females are usually the “Strong gender” [J Heart Lung Transplant. 2012 Oct; 31(10): 1045-1095]
- But...there is a significant correlation between gender and BOS
 - In our study males had more freedom from BOS and a better course of post-transplant disease.
 - This “gender gap”, in which females with CF appear to have higher morbidity and mortality than males, is hypothesized to be due to the pro-inflammatory effects of estrogens. [AU Sweezey NB et al. The cystic fibrosis gender gap: potential roles of estrogen. Pediatr Pulmonol. Apr 2014]

Discussion & Summary: Ethnicity

- Arab ethnicity was correlated with more BOS and shorter freedom from BOS.
- We don't know the reasons for these outcomes in the Arab population.
- Assuming no difference in adherence to treatment and follow-up...
- More passive smoking?

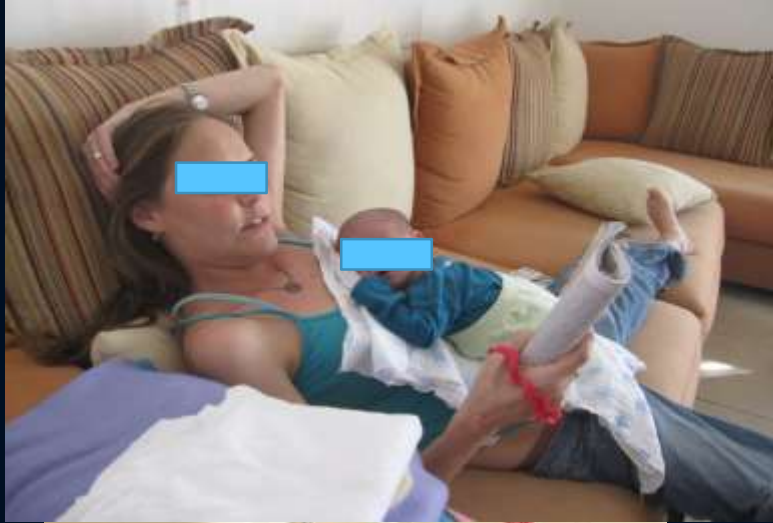
[Ethnic differences in patterns of secondhand **smoke** exposure among adolescents in Israel. Ben Noach M et. al. Nicotine Tob Res. 2012 Jun]

- Allen et al. presented that race matching resulted in an improvement in long-term survival. Maybe differences in donor ethnicity correlated with less freedom from BOS?

[Impact of donor-recipient race matching on survival after lung transplantation: analysis of over 11,000 patients. Allen JG et. al. J Heart Lung Transplant. 2009 Oct]

- Further study is necessary to investigate the impact of post-transplant management on survival in this population.

Happy Results!



THANKS!

