

**Patologia epatica in una prospettiva di genere**

**Modena 18 Giugno 2020**

**Trapianto di Fegato nell'ottica della  
Medicina di Genere: Problematiche  
Mediche e di Equita'**

**Patrizia Burra**

Multivisceral Transplant Unit, Gastroenterology

Department of Surgery, Oncology and Gastroenterology

Padua University Hospital

Padua



# Influence of gender in liver transplantation

Access to the waiting list

Waiting list mortality

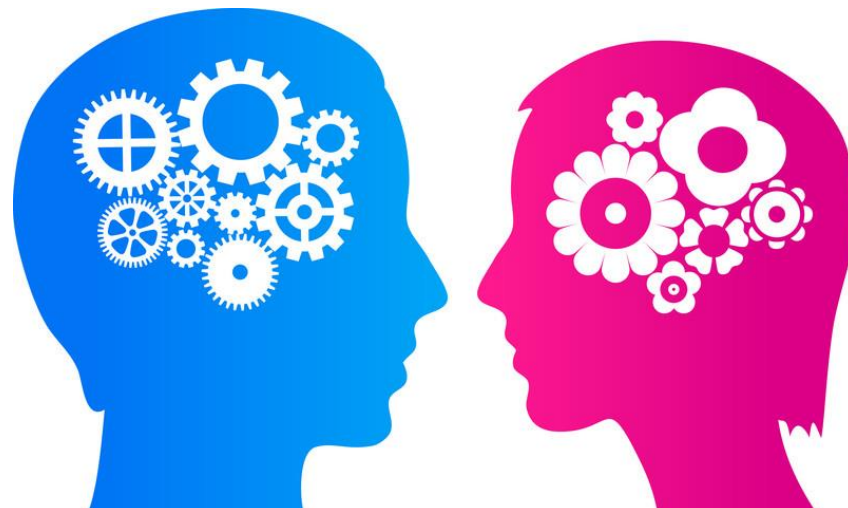
Transplant rates

Complications

Quality of life

Patient and graft survival

Sexual dysfunction



# Influence of gender in liver transplantation

Access to the waiting list

Waiting list mortality

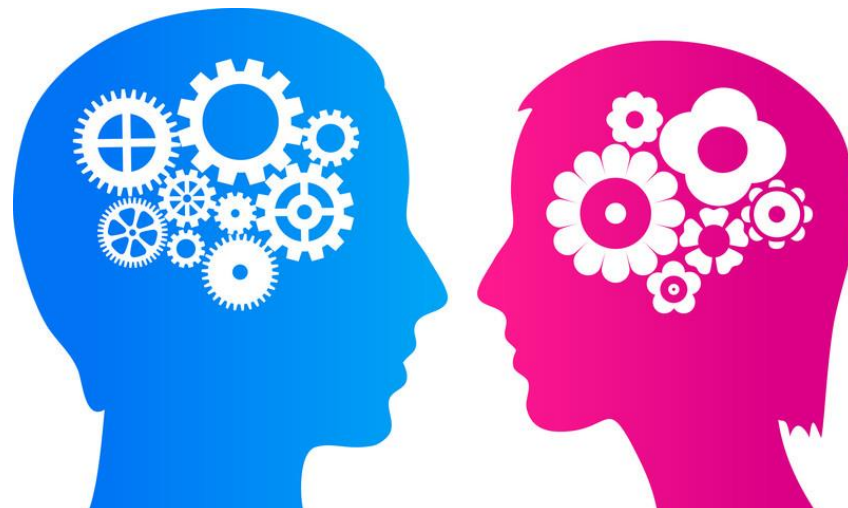
Transplant rates

Complications

Quality of life

Patient and graft survival

Sexual dysfunction



In an era of organ shortage, who get the liver and who die in the waiting list ?



?

In an era of organ shortage, who get the liver and who die in the waiting list ?



**Mean annual waiting list mortality = 10.2%**

In an era of organ shortage, who get the liver and who die in the waiting list ?

**Female = 18%**  
(Relative risk 1.9;  
 $p=0.0026$ )

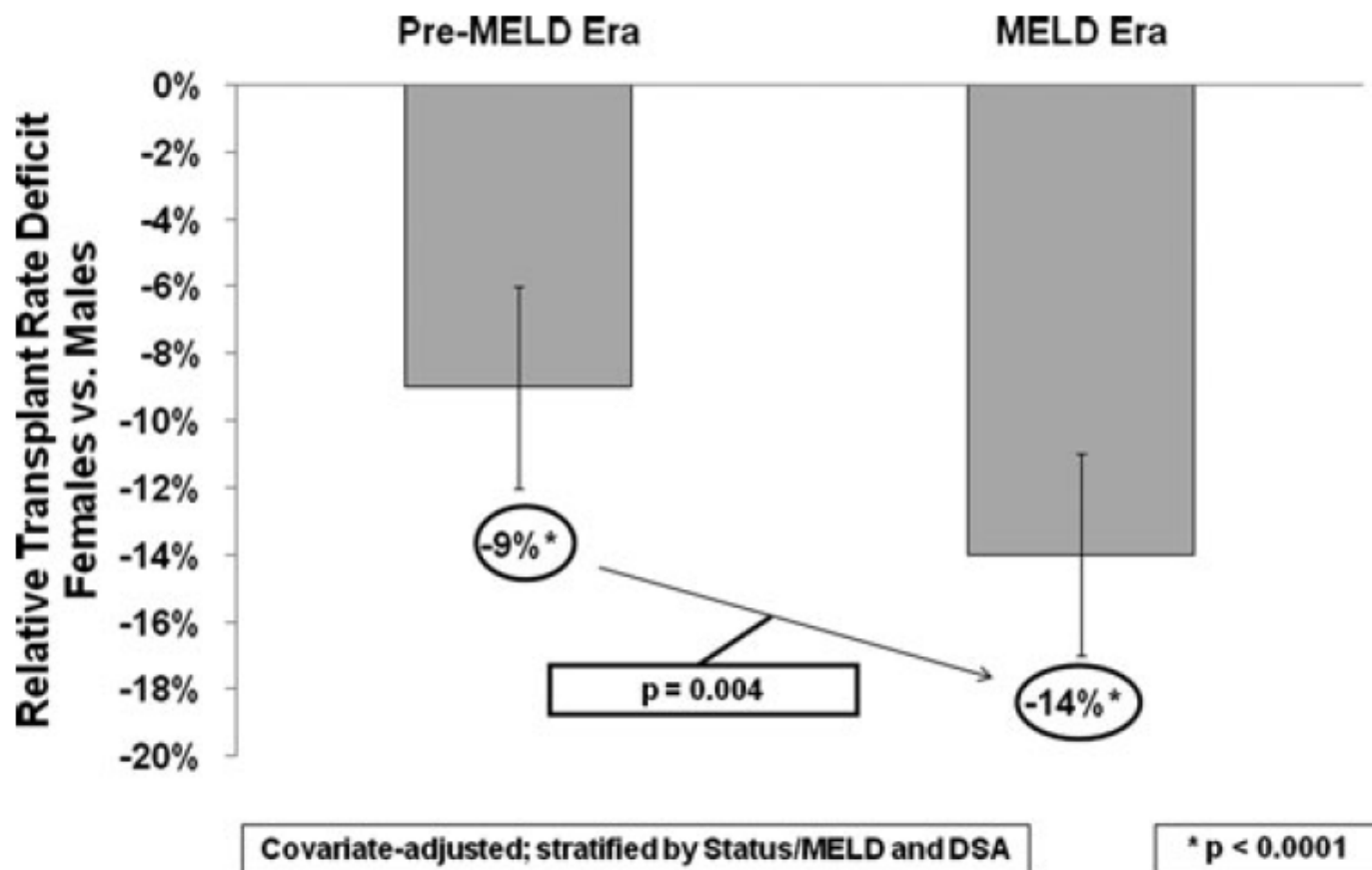


**Male = 9%**

**Mean annual waiting list mortality = 10.2%**

# Females have lower transplant rates before and after MELD (creatinine, INR, bilirubin) era

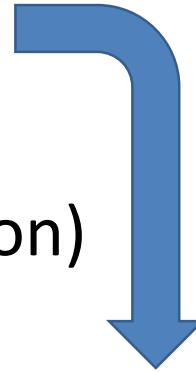
UNOS LT waiting list  
N= 78.998



# Why Gender Disparity with MELD (creatinine, bilirubin, INR)?

Compared with Men, Women had:

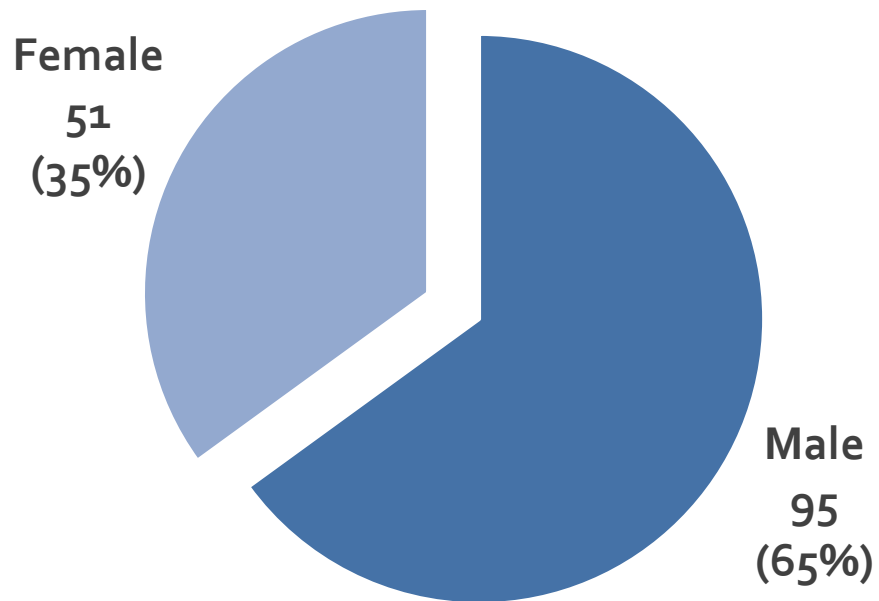
- 1) lower creatinine (lower MELD)
- (2) lower eGFR (worse renal function)
- (3) higher bilirubin and INR (worse liver function)



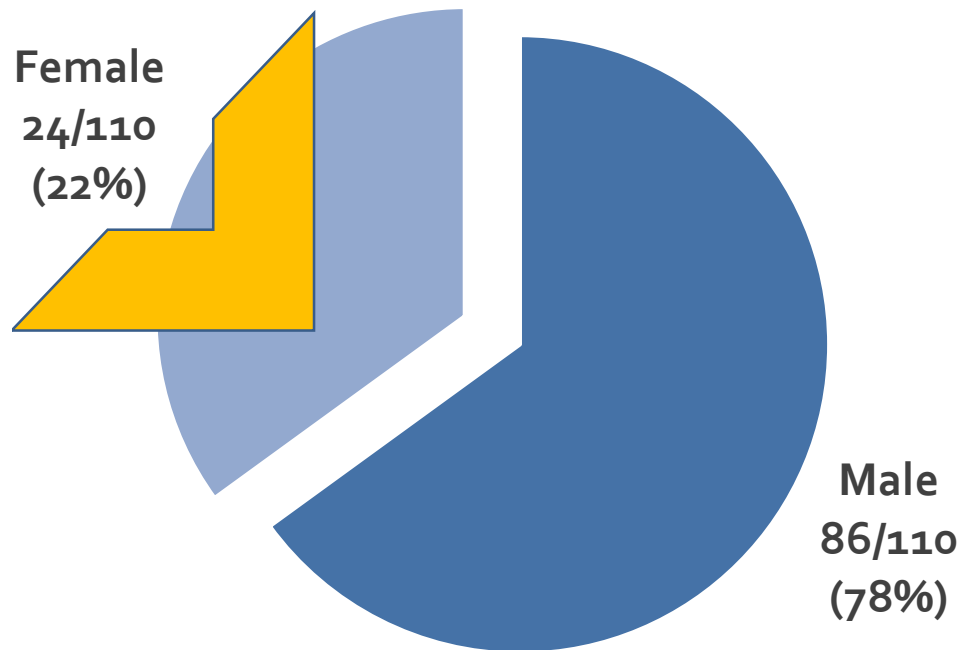


# Padua Liver Transplant Center -2017-

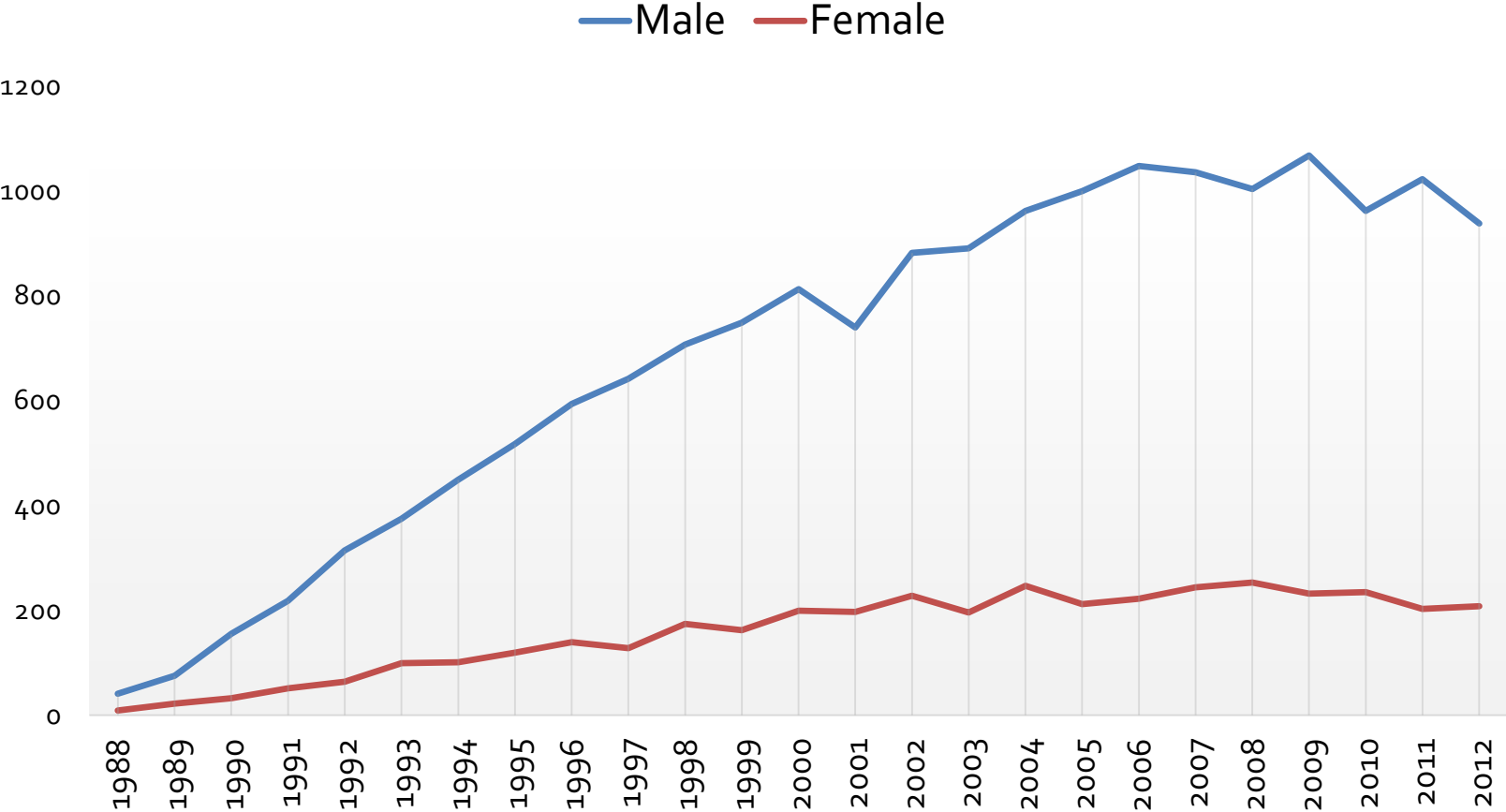
## Listed



## Transplanted



# Number of liver transplants overtime according to recipient gender in Alcohol-related Liver Disease (ALD) patients



Germani G, Villa E, Burra P et Al. Liver Int 2020

# Donor graft quality and gender

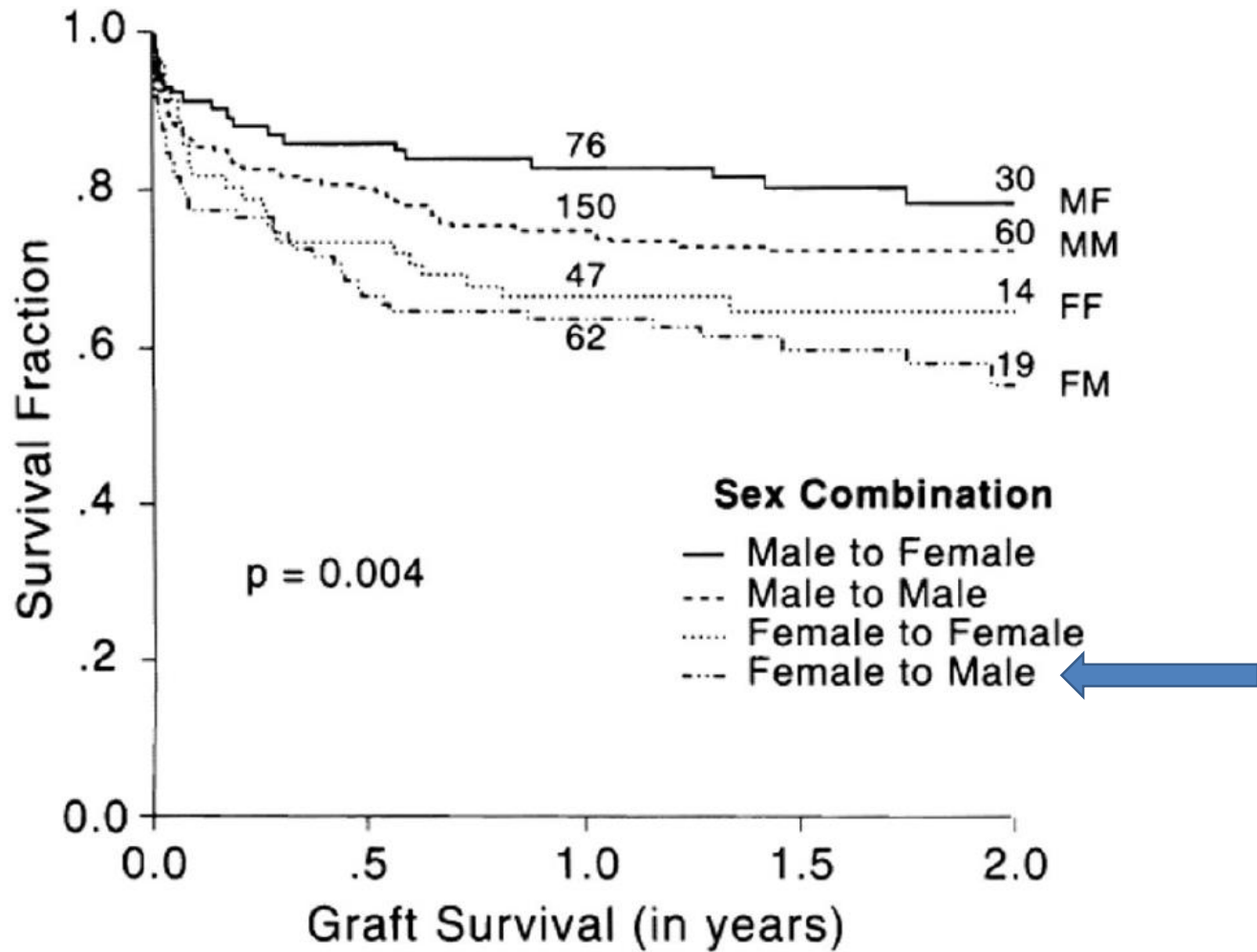
Donor quality differs significantly between female and male donor, since female donors are:

- older
- shorter
- die more frequently of stroke

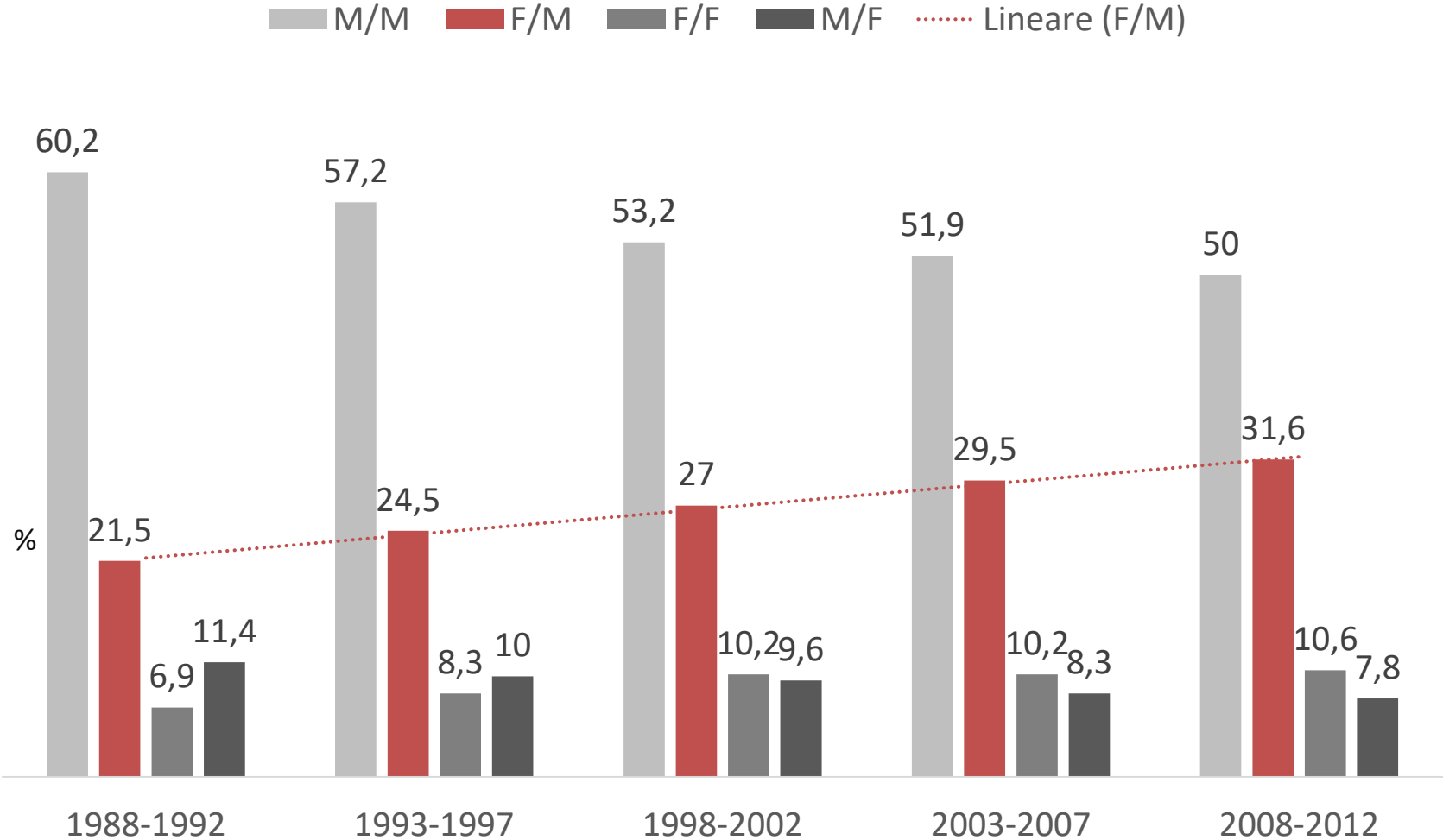
Probably gender differences in donor quality, rather than gender mismatch are predictive of graft loss.

# Donor/recipient gender mismatch

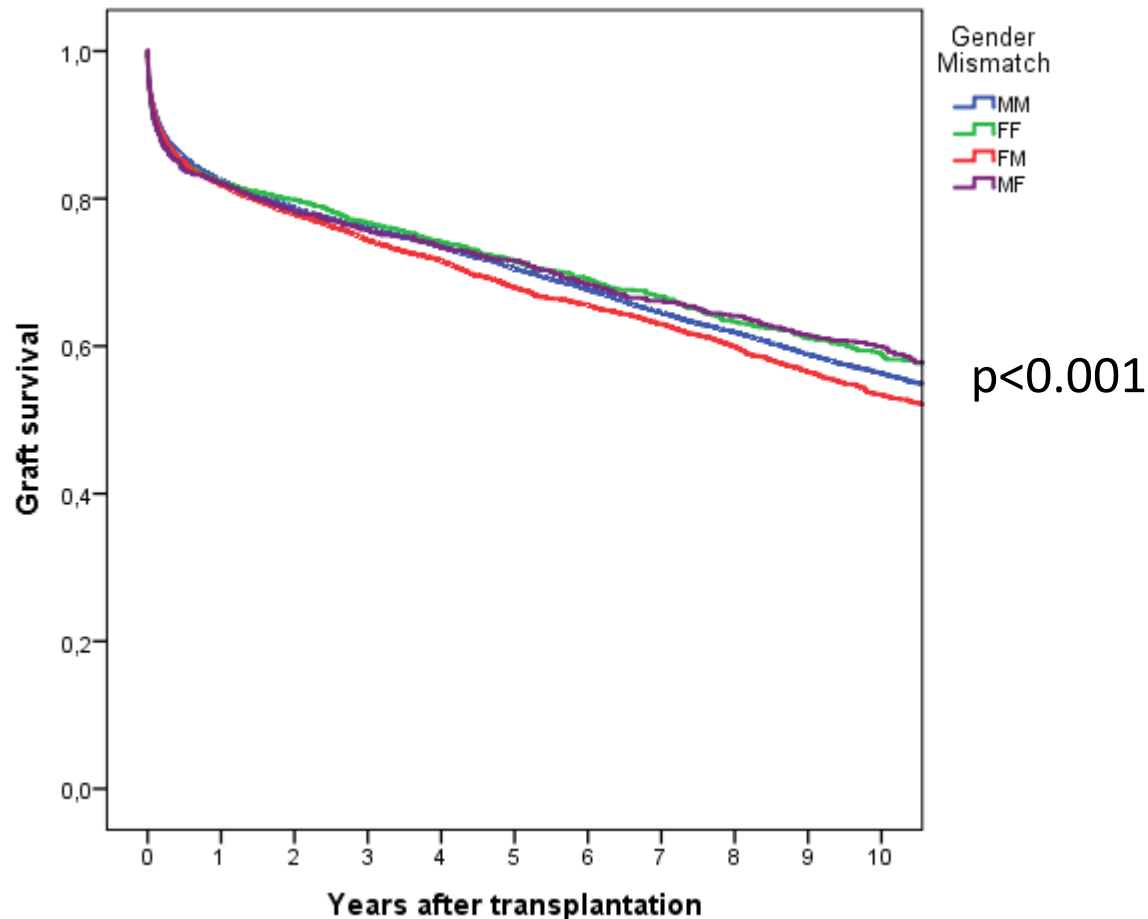
Graft survival according to donor-recipient sex combination



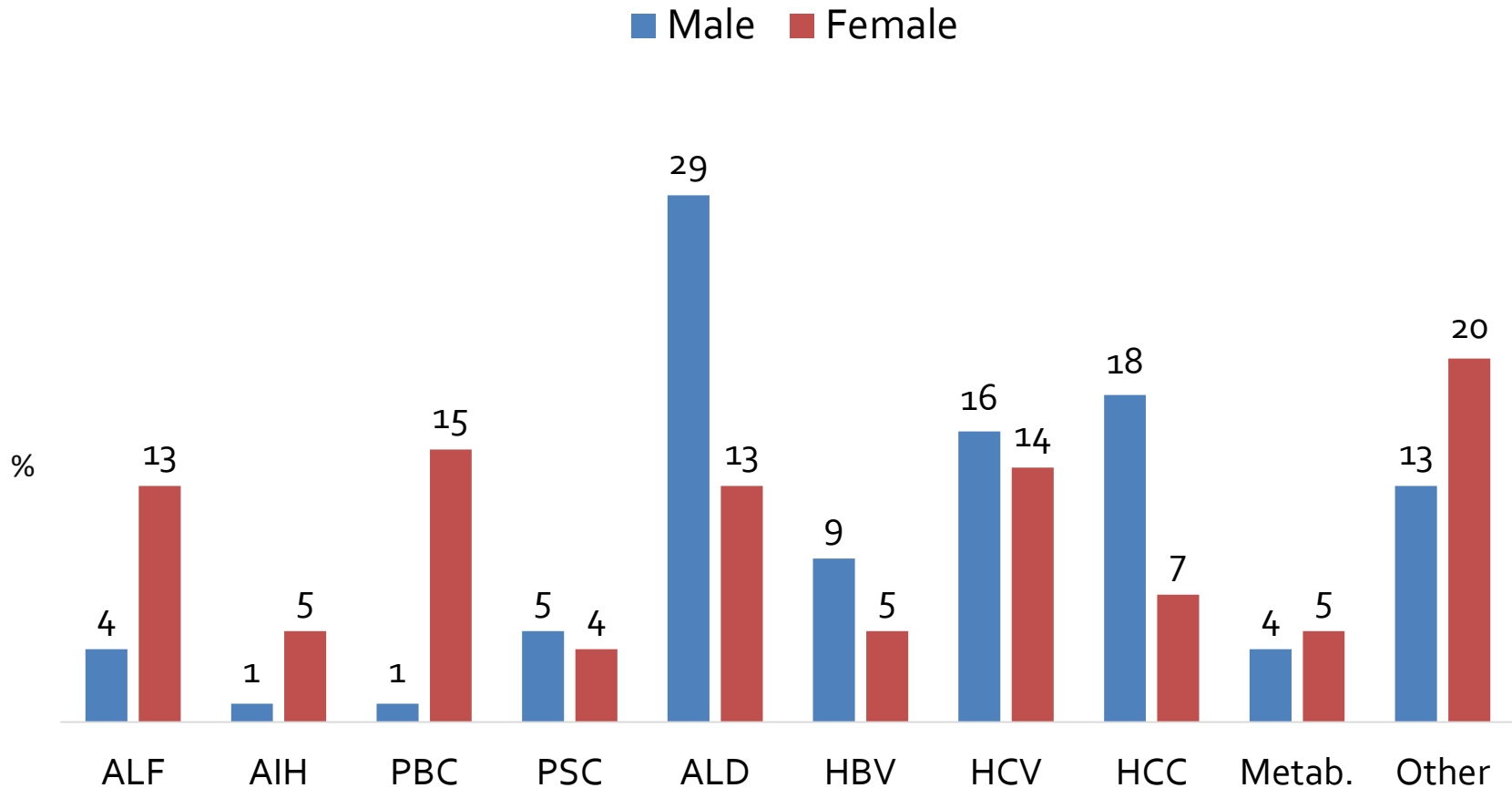
# Changes in donor/recipient gender matching overtime in ALD patients



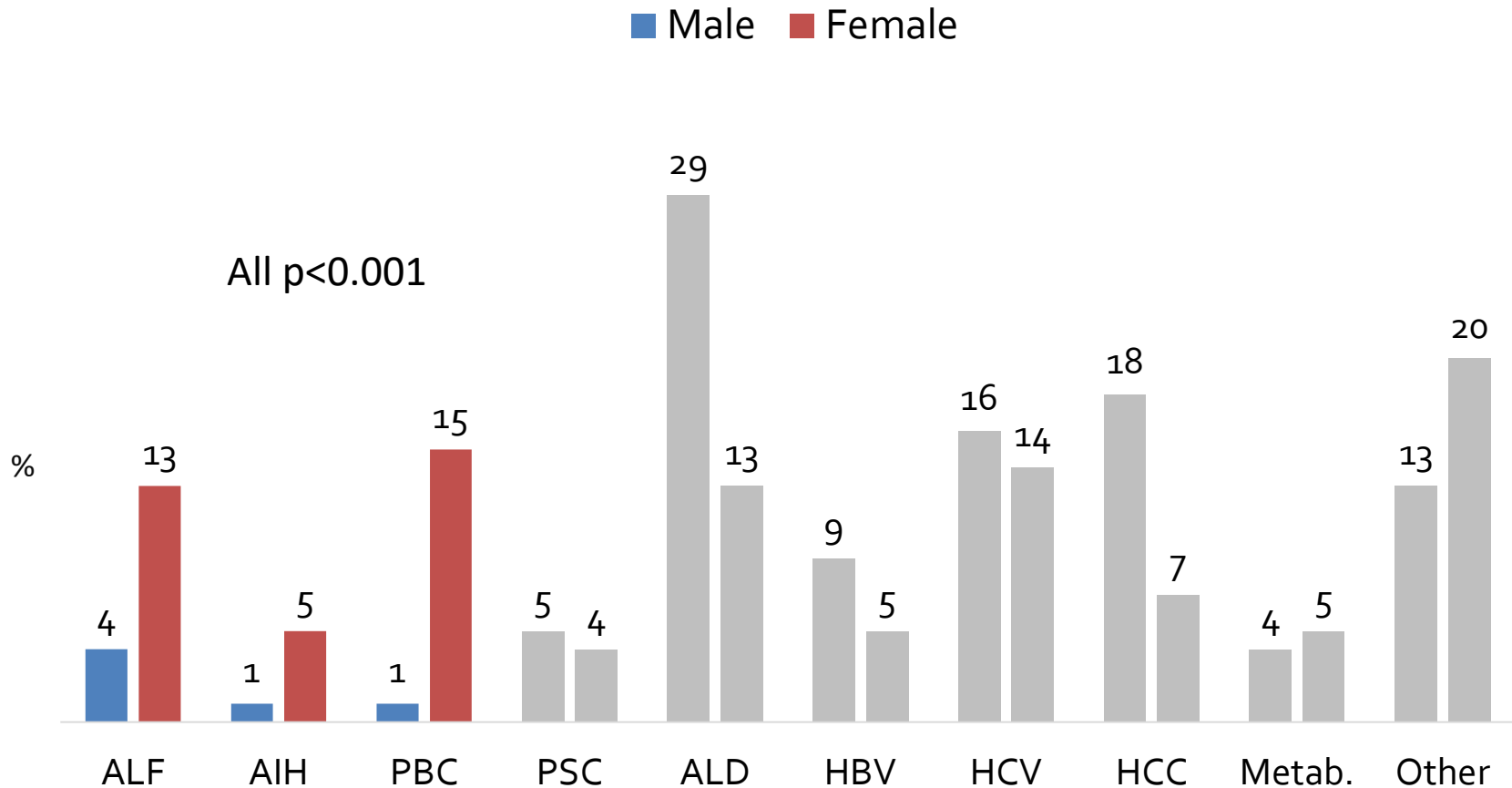
# Graft survival according to donor/recipient gender matching in ALD patients



# Indications to liver transplantation according to recipient gender

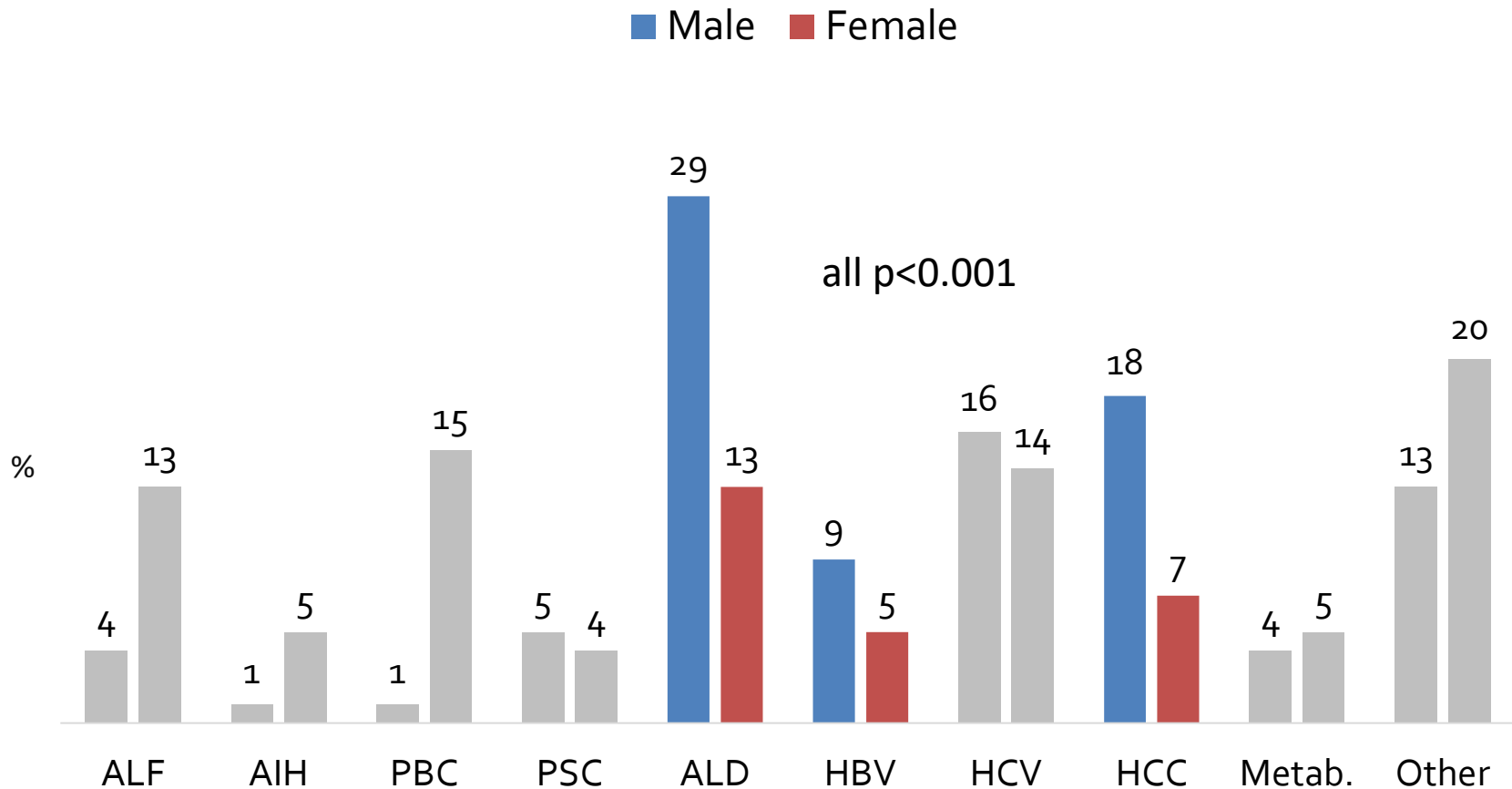


# Indications to liver transplantation according to recipient gender





# Indications to liver transplantation according to recipient gender



# Influence of gender in liver transplantation

Access to the waiting list

Waiting list mortality

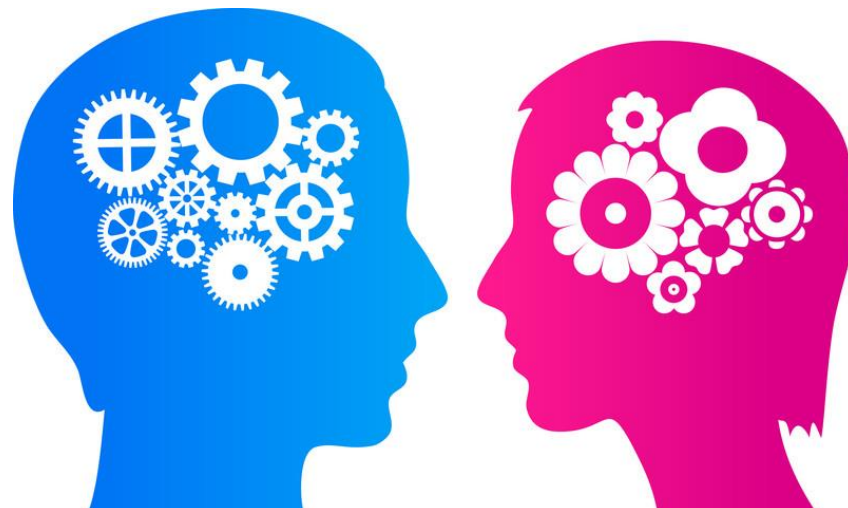
Transplant rates

Complications

Quality of life

Patient and graft survival

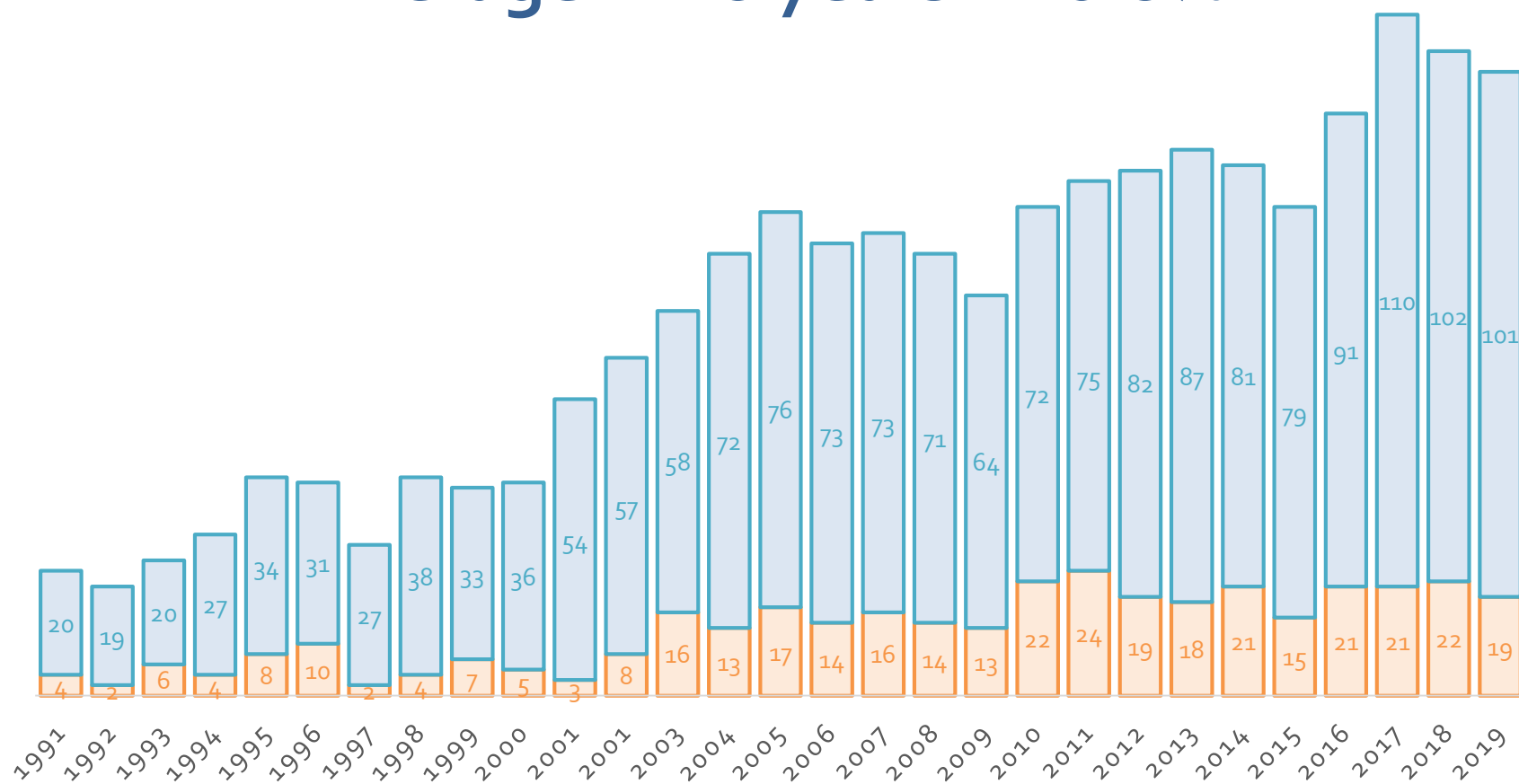
Sexual dysfunction



# Liver transplantation for alcohol-related liver disease: Padua experience (1991-2019)

ALD

Average in 28 years = 20.8%



# Alcohol relapse after transplantation

Relapse rate of harmful alcohol consumption=10%

## ***Univariate analysis:***

pretransplant abstinence <6 months (P=0.003)

psychiatric comorbidities (P=0.016)

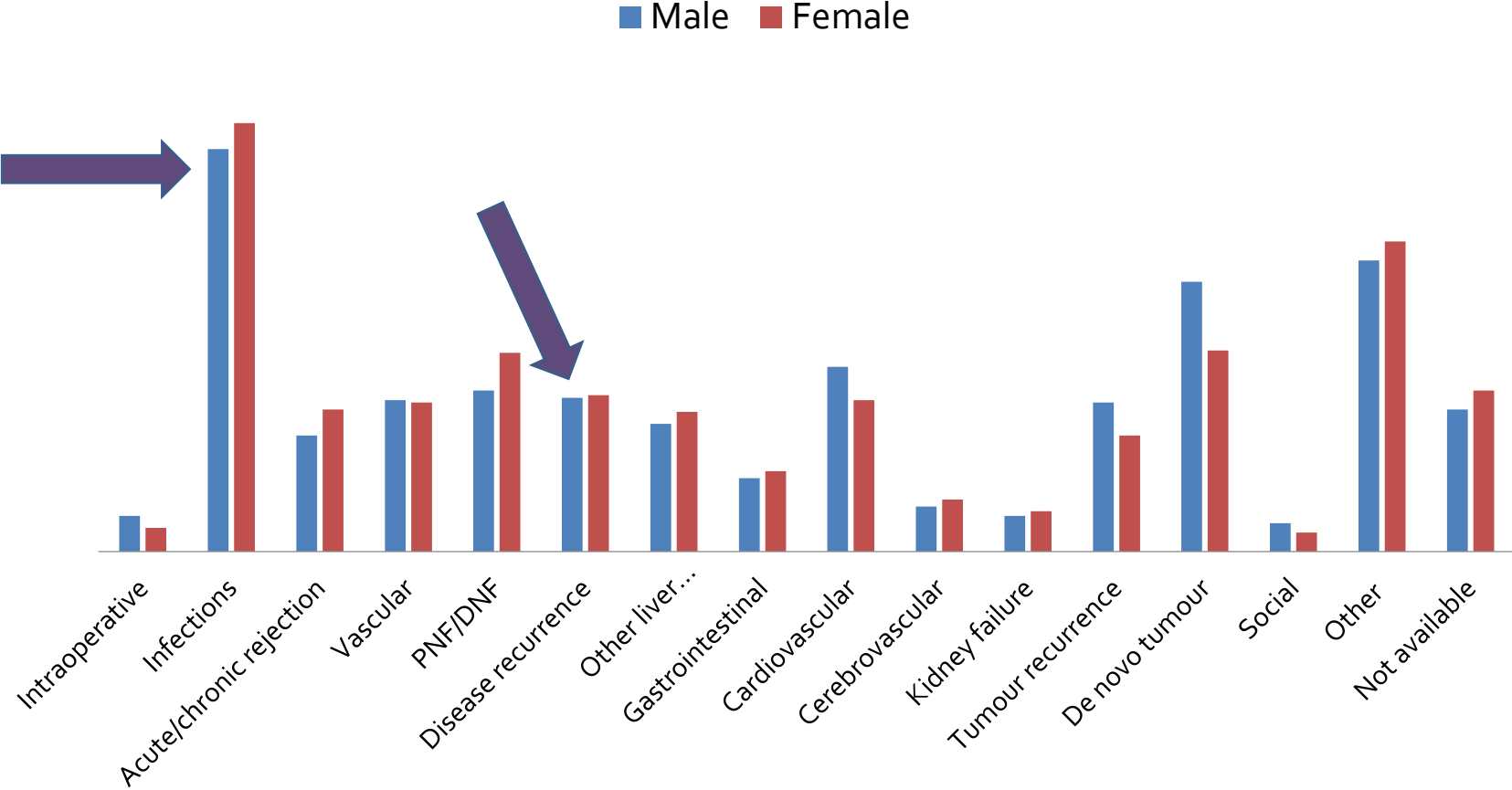
**female sex (P=0.019)**

## ***Multivariate logistic regression analysis:***

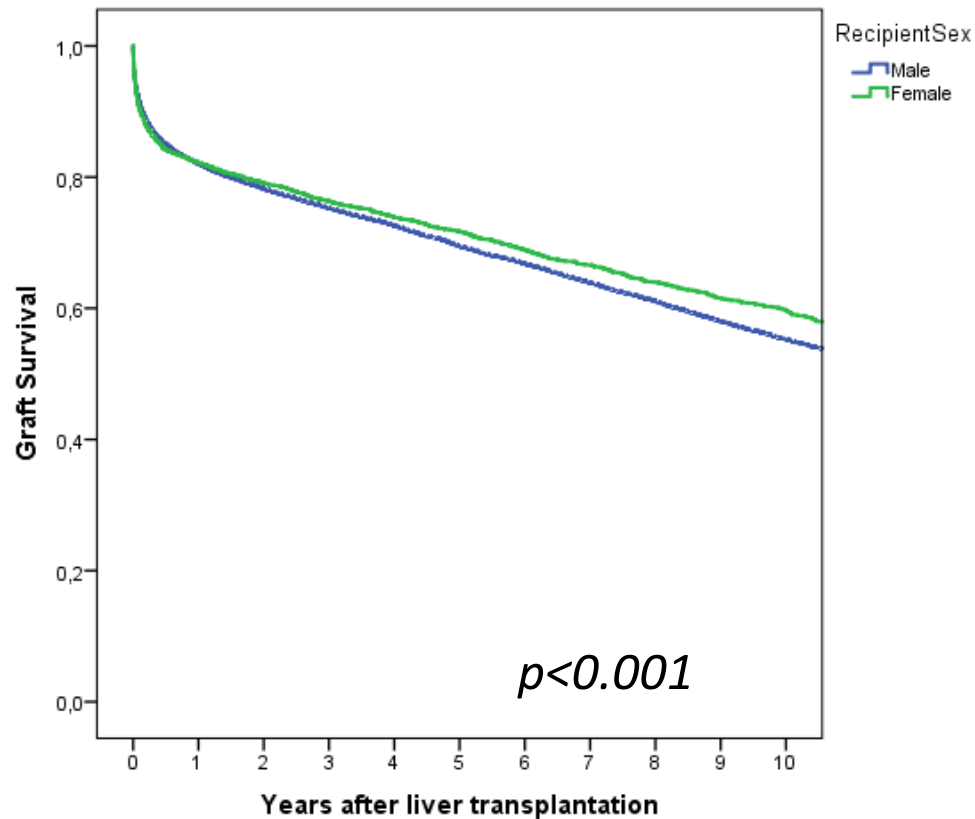
pretransplant abstinence < 6 months (OR 77.07; standard error 1.743; P=0.013)

**female sex (OR 18.80; standard error 1.451; P=0.043)**

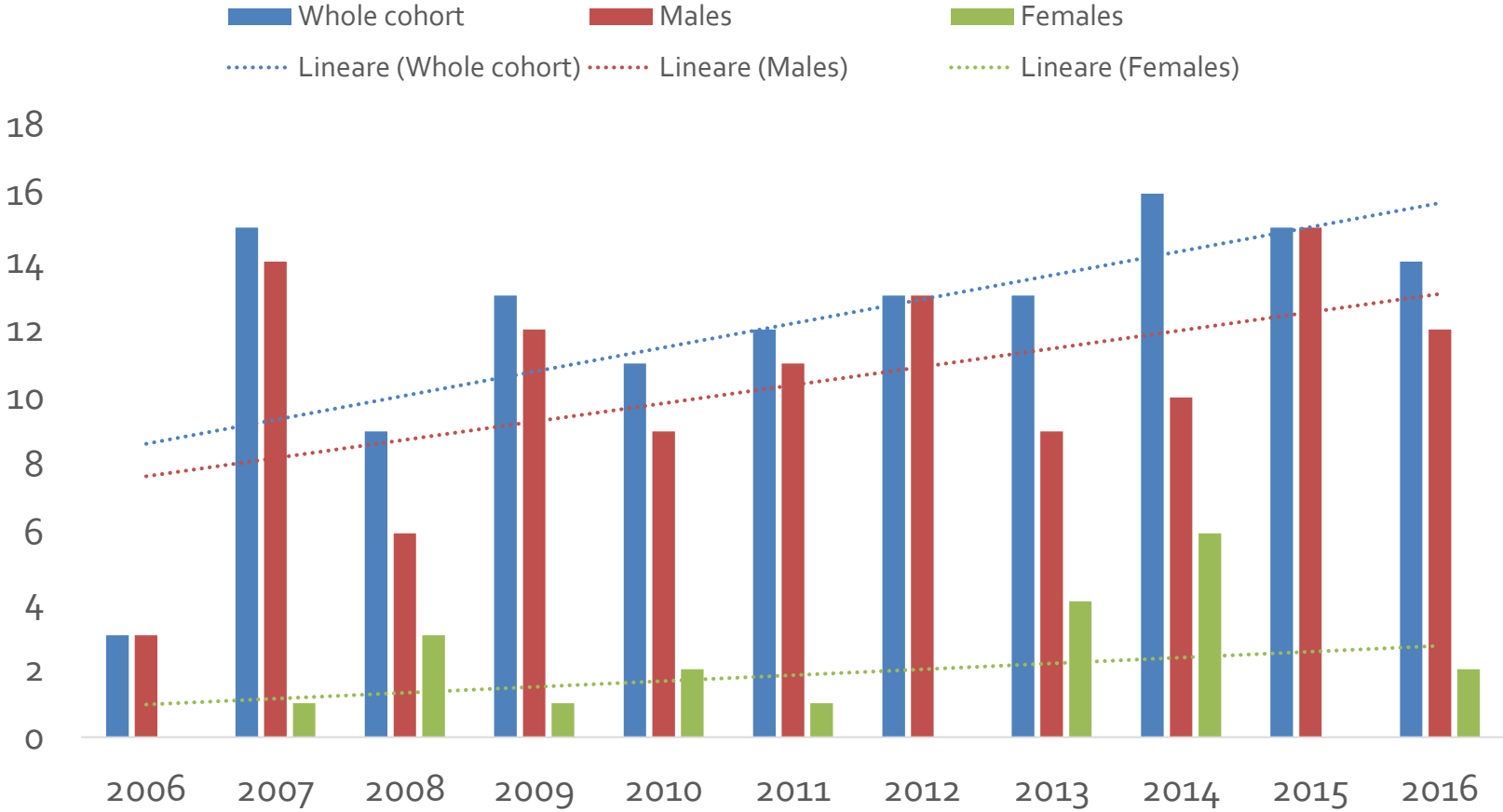
# Causes of death/graft loss according to recipient gender in ALD patients



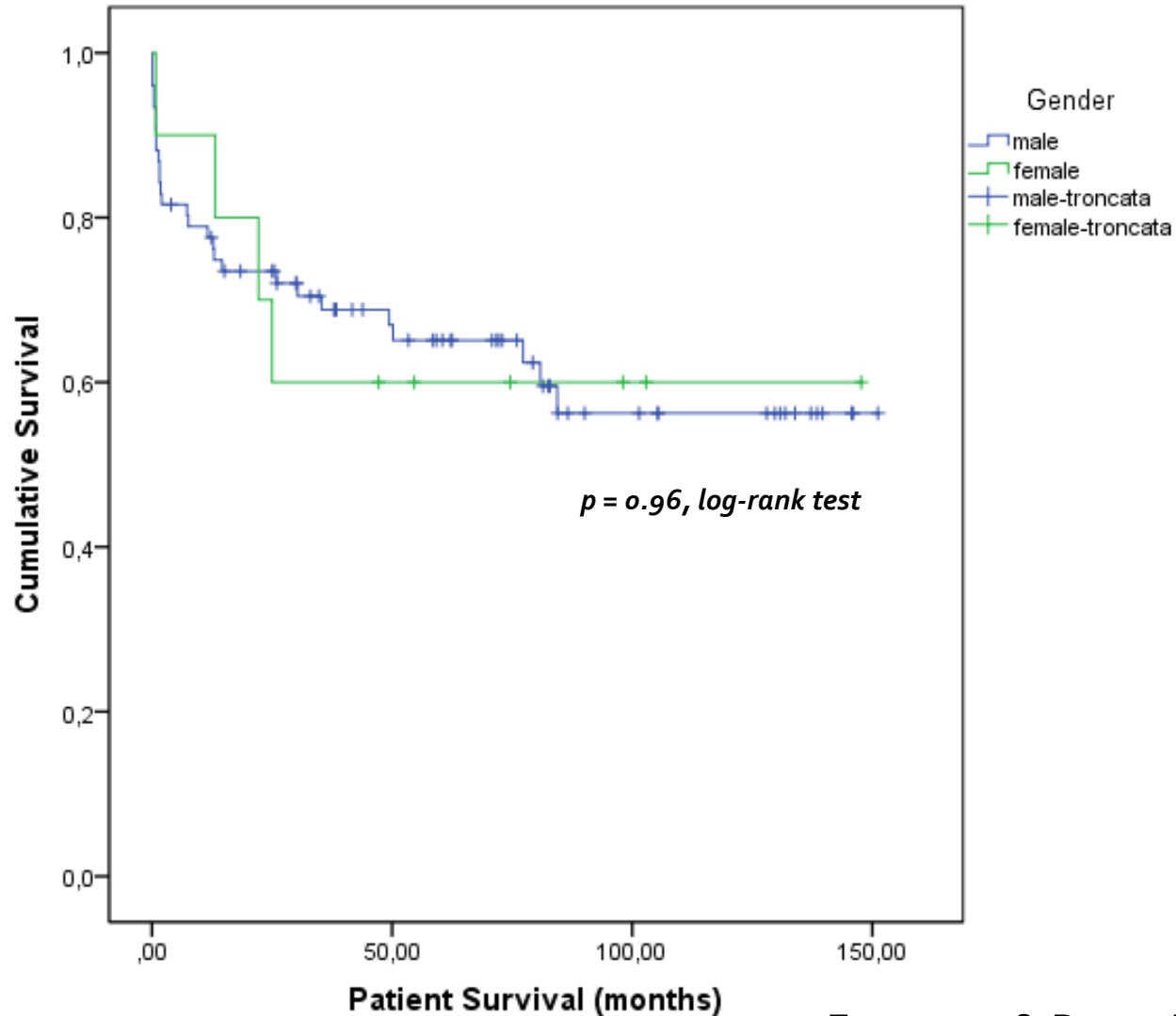
# Better graft survival in female vs male after transplantation for alcoholic liver disease



# Increased liver transplantation rate for HCC overtime in males in Padua in 10 years

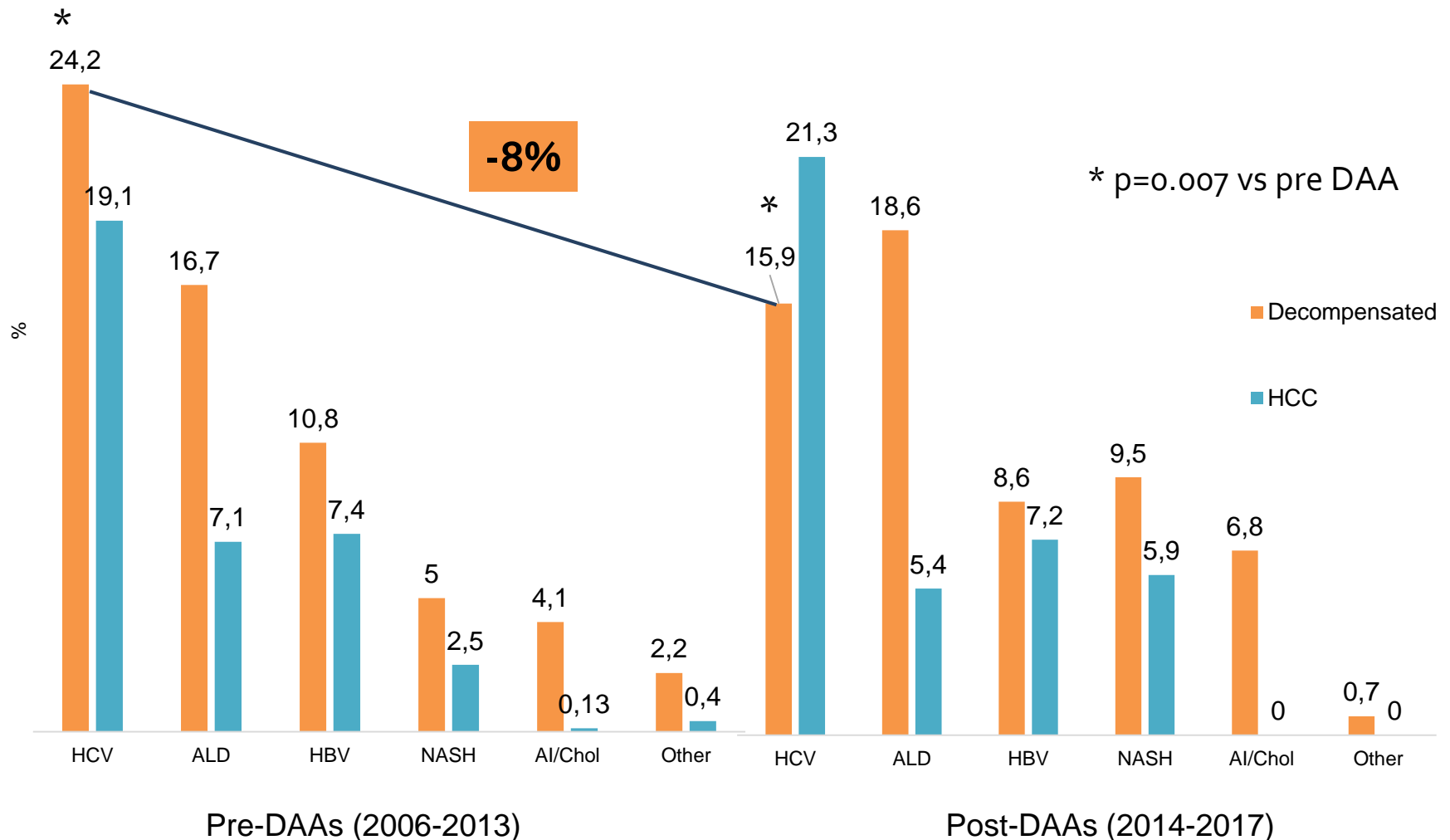


# Long-Term Patient Survival in patients transplanted for HBV-related cirrhosis according to gender - Padua University Hospital -

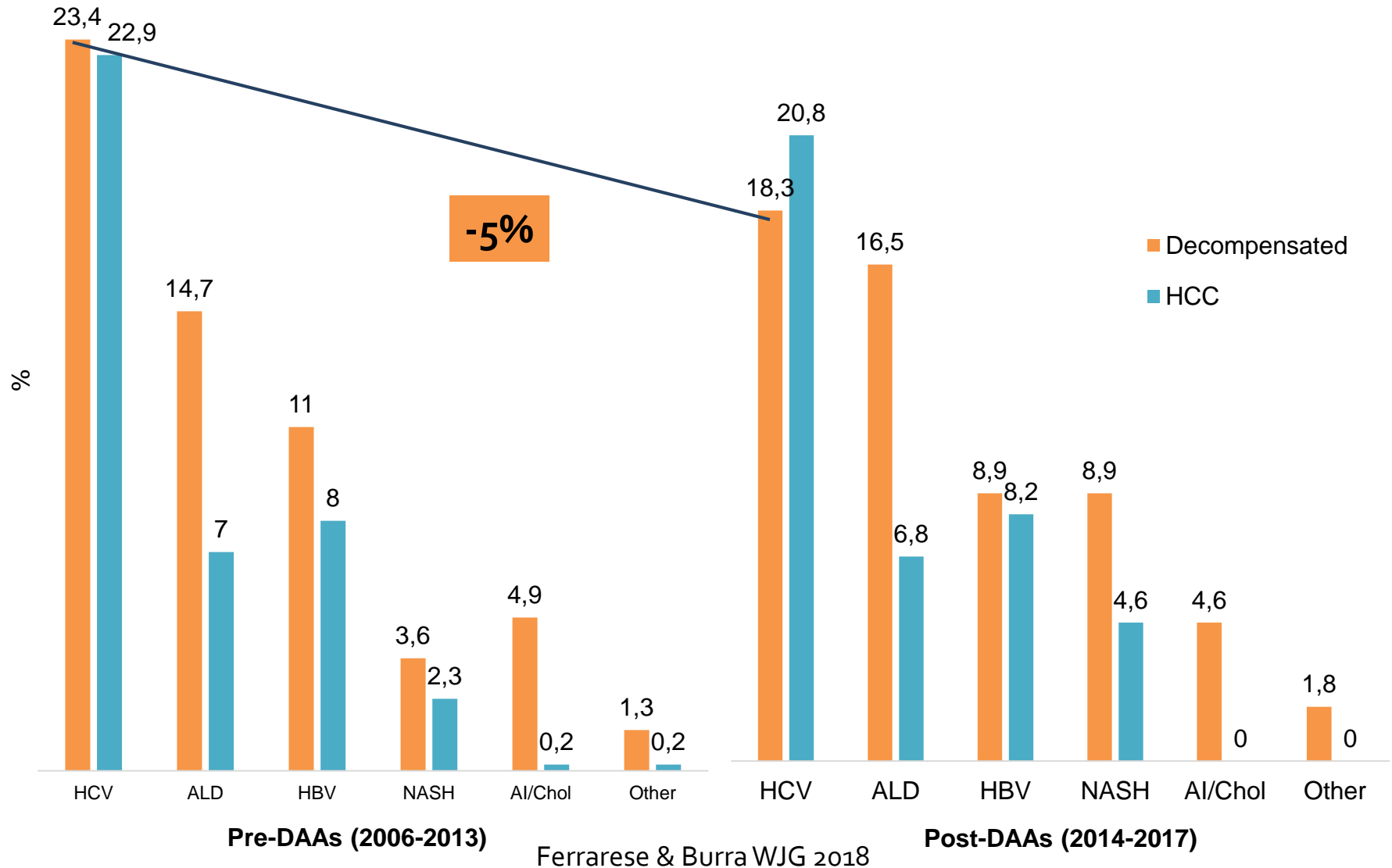




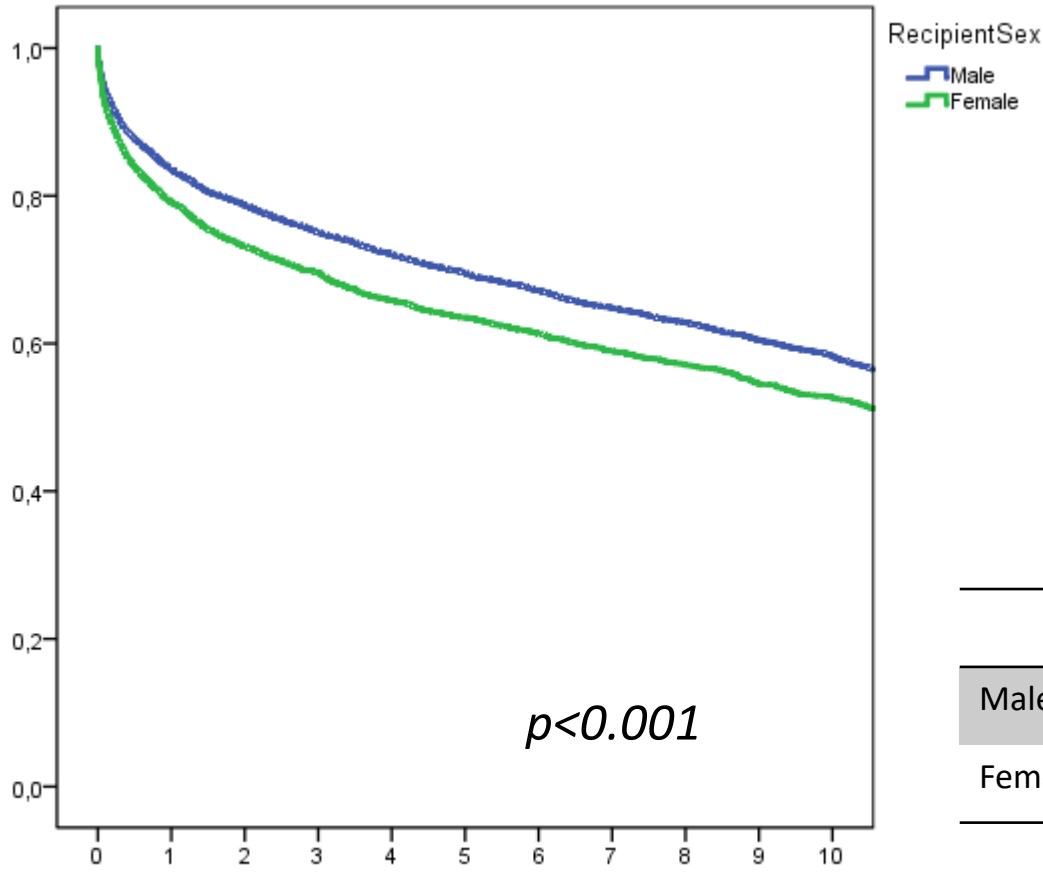
# Changing scenario on waiting list registrations before and after new antivirals for HCV (DAAs) Padua University Hospital Experience



# Liver Transplantation before and after DAAs introduction Padua University Hospital Experience

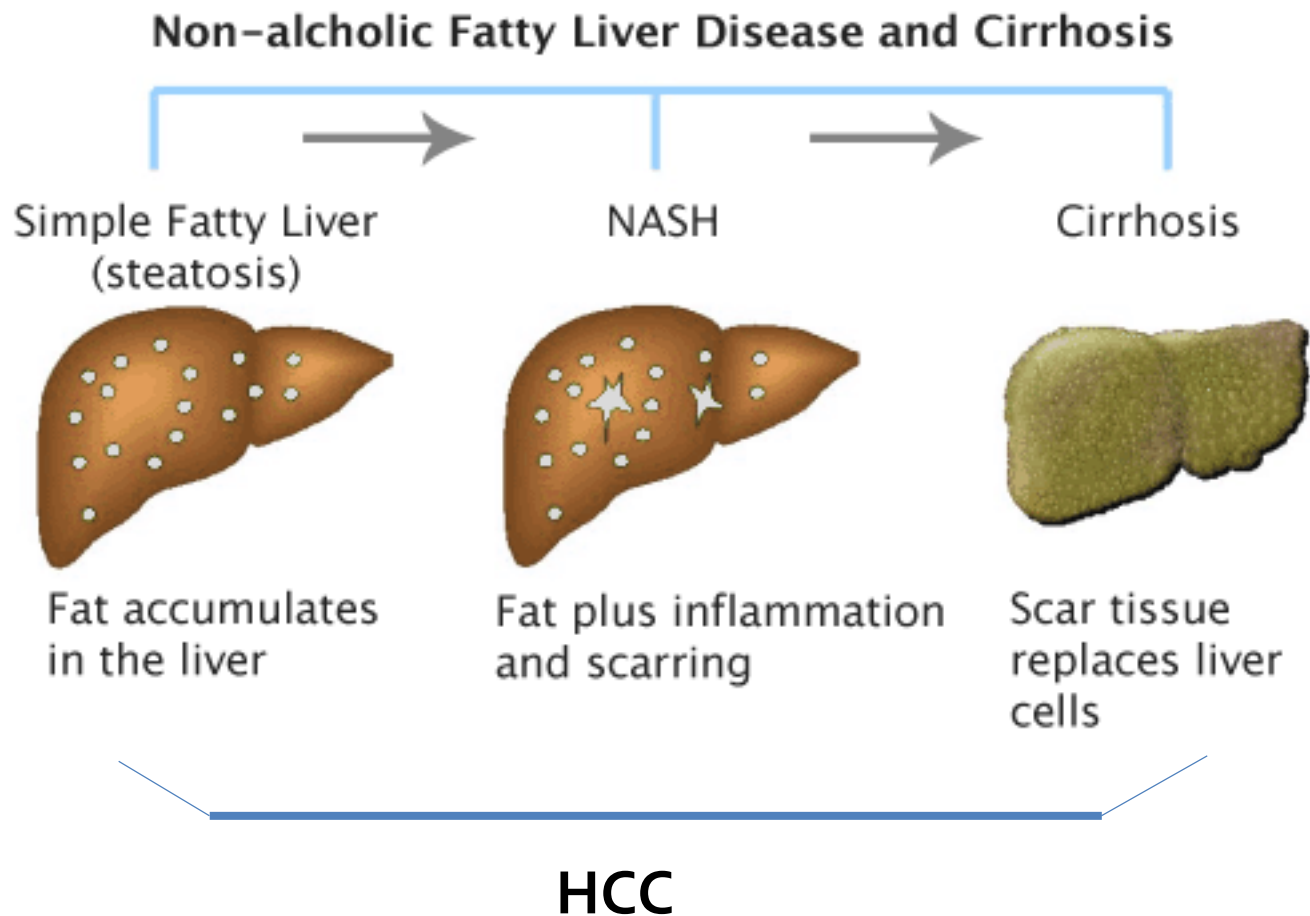


# Worse graft survival in HCV positive female vs male liver transplant recipients



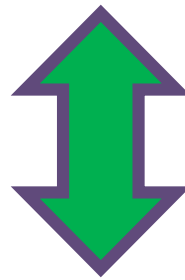
	1 year	3 years	5 years	10 years
Male	72%	65%	59%	47%
Female	67%	60%	55%	44%

# The natural history of non-alcoholic fatty liver disease



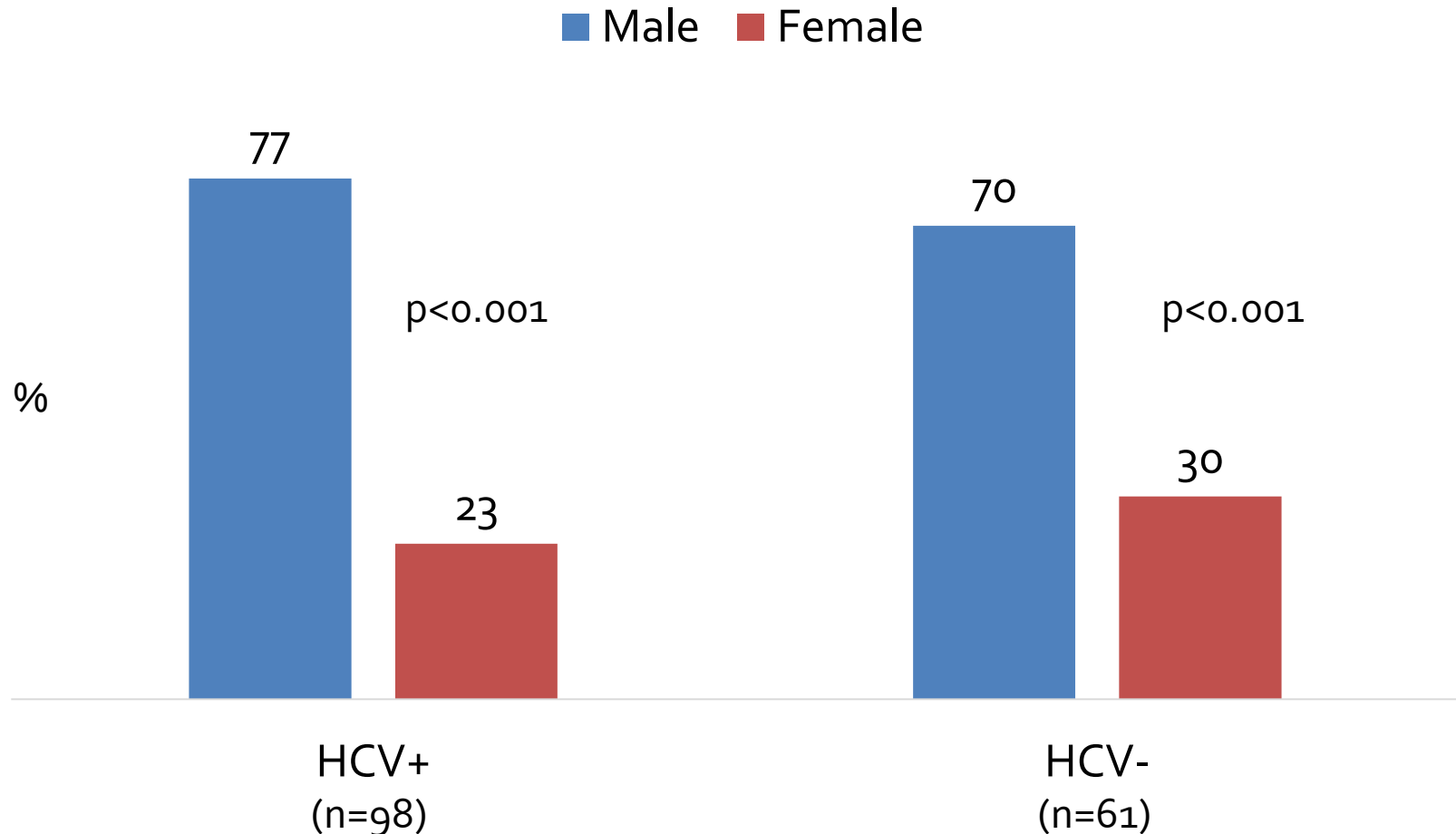
**PRE-TRANSPLANT**

**NASH**  
**NAFLD**



**POST-TRANSPLANT**  
**Recurrence**  
**De novo**

# De novo metabolic syndrome in 98 HCV+ and 61 HCV- recipients according to recipient gender



## Prevalence of the components of metabolic syndrome before and after liver transplantation: Padua experience

	Pre-LT	6-months post-LT	P value*	12-months post-LT	P value*	24-months post-LT	P value*
<b>Obesity</b>	18 (27%)	15 (26%)	1.00	24 (38%)	0.267	23 (36%)	0.26
<b>IFG</b>	17 (27%)	18 (29%)	1.00	18 (29%)	1.00	21 (33%)	0.557
<b>DMII</b>	<b>10 (16%)</b>	21 (33%)	<b>0.003</b>	21 (33%)	<b>0.003</b>	<b>21 (33%)</b>	<b>0.003</b>
<b>Hypertension</b>	<b>8 (13%)</b>	24 (38%)	<b>&lt; 0.001</b>	23 (37%)	<b>0.001</b>	<b>19 (30%)</b>	<b>0.013</b>
<b>Hypertriglyceridemia</b>	<b>9 (14%)</b>	20 (31%)	<b>0.035</b>	24 (38%)	<b>0.006</b>	<b>15 (24%)</b>	0.263

# Menopause and metabolic syndrome

In a long term observational study metabolic syndrome **was a significantly risk of mortality**, in a period of 12 years, **for postmenopausal women**, compared to men and premenopausal women.



# Cardiovascular diseases

Coronary artery disease in women increases at the onset of **menopause** due to the loss of female sex hormones.

Trapani, Current Gerontology and Geriatrics Research 2010

Yanes, American Journal of Hypertension 2011

# Osteoporosis and bone fractures

After liver transplantation, bone turnover is increased.

Immunosuppressive drugs are responsible for bone loss.

Bone fractures rates range from 24%-65% after liver transplantation.

Women with **PBC and severe preexisting bone disease** appear to be at greatest risk of osteoporosis and bone fractures after liver transplantation.

## Causes of death/graft loss according to recipient gender

	Male (n = 32 656)	Female (n = 13 678)	p-value
Intra-operative, %	2.2	1.7	ns
Infections, %	21.7	24.1	ns
Acute/chronic rejection, %	2.2	2.2	ns
Vascular, %	3.7	3.8	ns
PNF/DNF, %	2.7	3.6	.03
Disease recurrence, %	10.7	13.3	<.001
Liver complication— other, %	3.1	2.9	ns
Gastrointestinal, %	3.5	3.6	ns
Cardiovascular, %	7.3	7.3	ns
Cerebrovascular, %	4.2	3.8	ns
Tumour recurrence, %	14.4	10.1	<.001
Tumour de novo, %	7.7	5.1	<.001
Other, %	12.2	12.9	ns
Not available, %	4.4	5.6	ns



# Influence of donor and recipient gender on liver transplantation outcomes in Europe: factors associated with lower survival

## FEMALE

Donor BMI >30 (p=0.005)

Donor age >60 years (p=0.027)

Recipient age (p=0.0001)

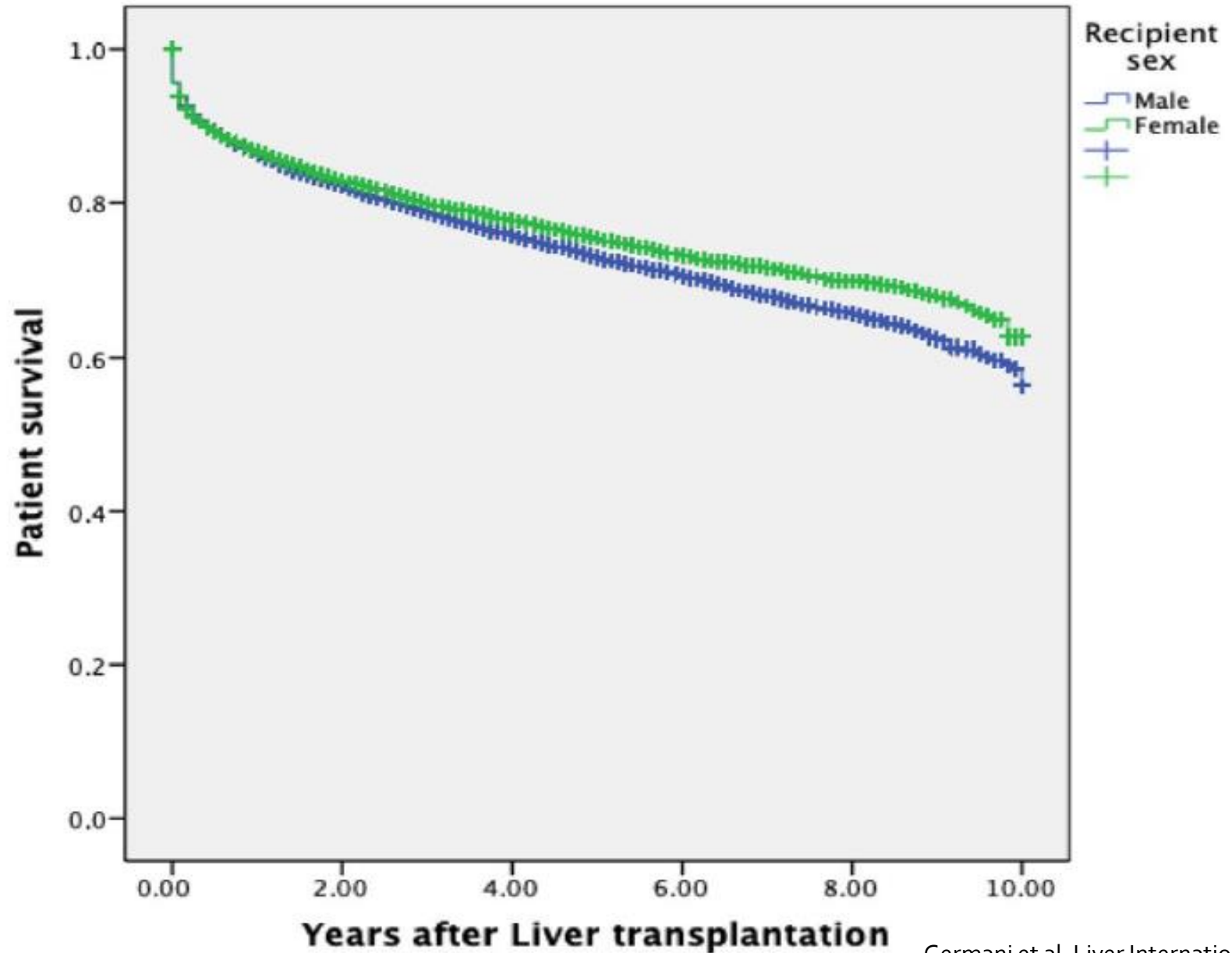
## MALE

Donor/recipient gender mismatch (p=0.003)

Donor age >60 years (p=0.027)

Recipient age (p=0.0001)

## Patient survival after liver transplantation according to recipient gender (Log-Rank $P < .0001$ )



# Influence of gender in liver transplantation

Access to the waiting list

Waiting list mortality

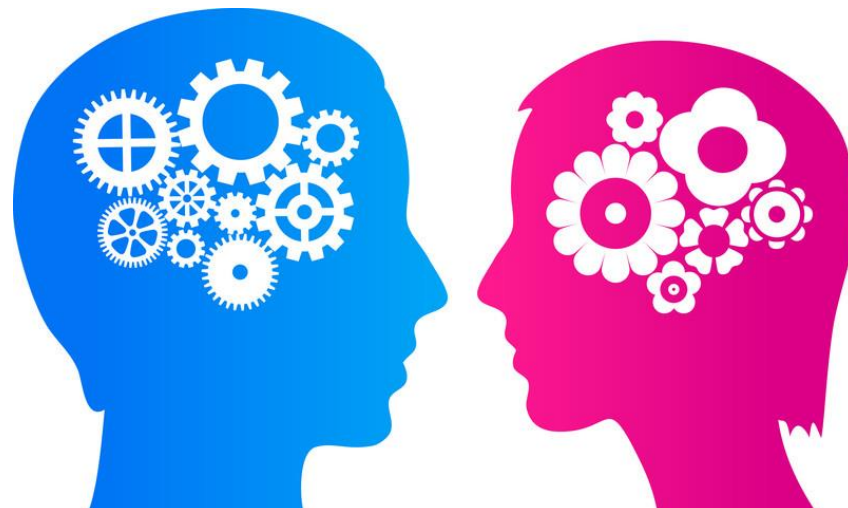
Transplant rates

Complications

Quality of life

Patient and graft survival

Sexual dysfunction



# Quality of life

Effects of gender on quality of life, conflicting data.

(Tome Journal of Hepatology 2008)

Men lower quality of life than female recipients.

(Kober Psychother Psychosom 1990)

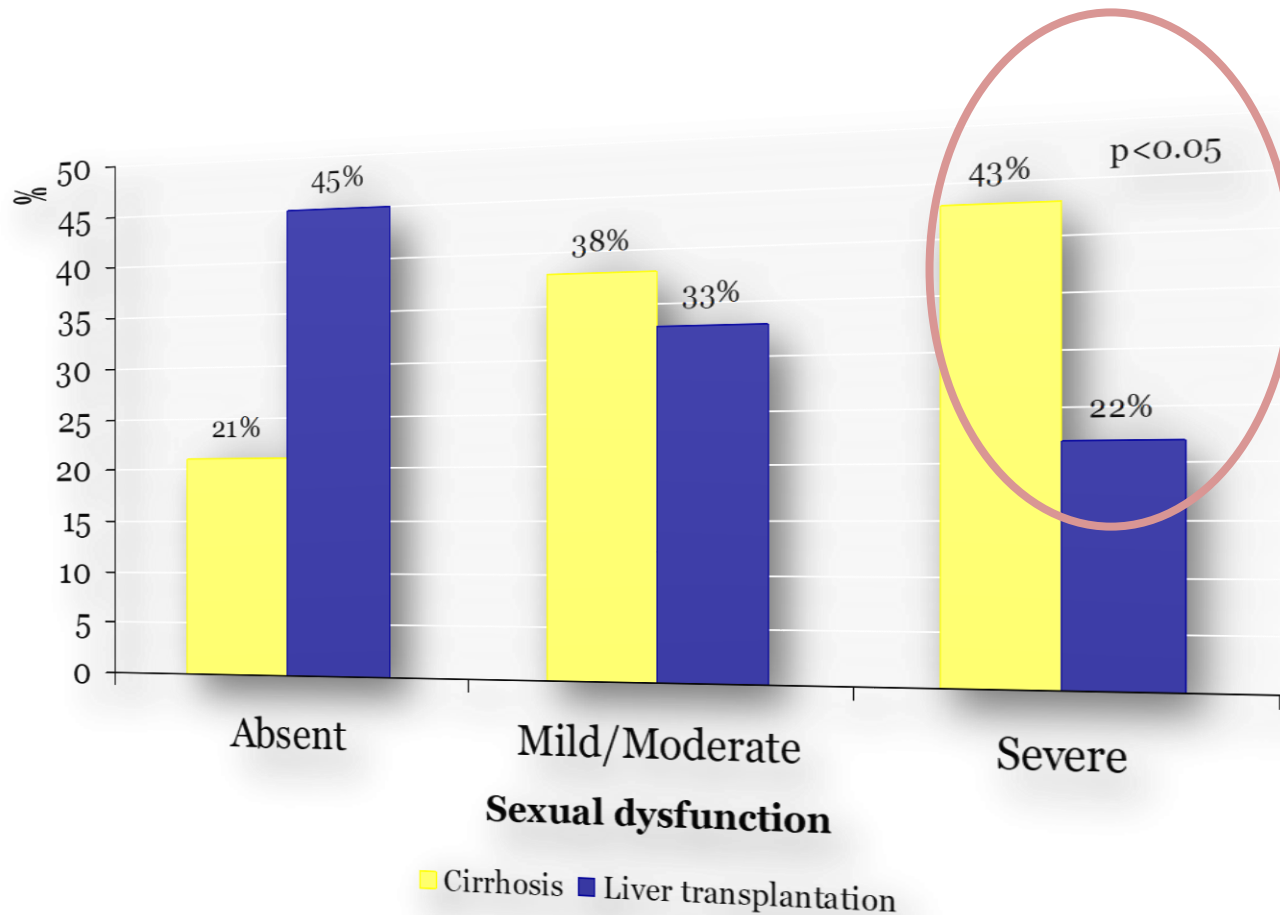
The largest study to date reported that female gender lowers quality of life scores after liver transplant.

(Cowling Ann Surg 2004)

No significance differences.

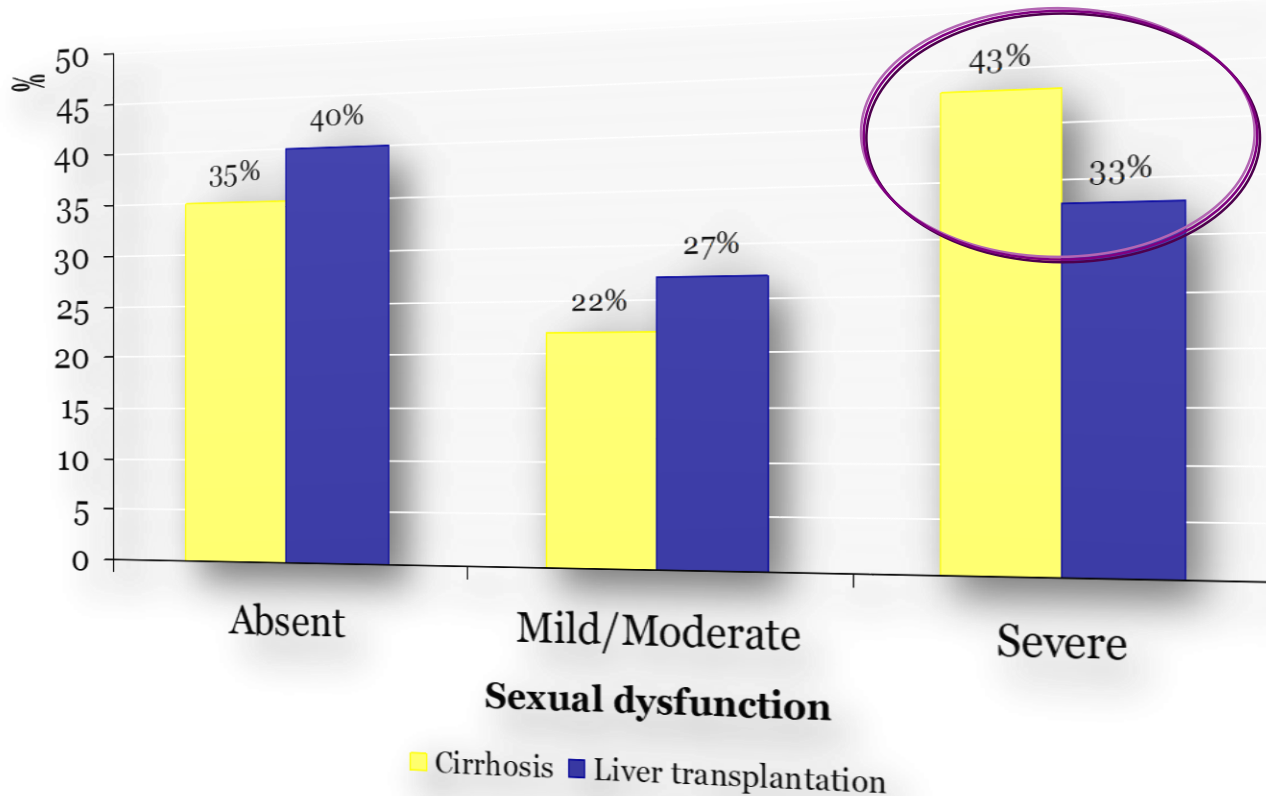
(Bravata Liver Transplantation 2001, Moore Liver Transplantation 2000)

## Sexual dysfunction in 129 men with liver cirrhosis and 123 men after liver transplantation

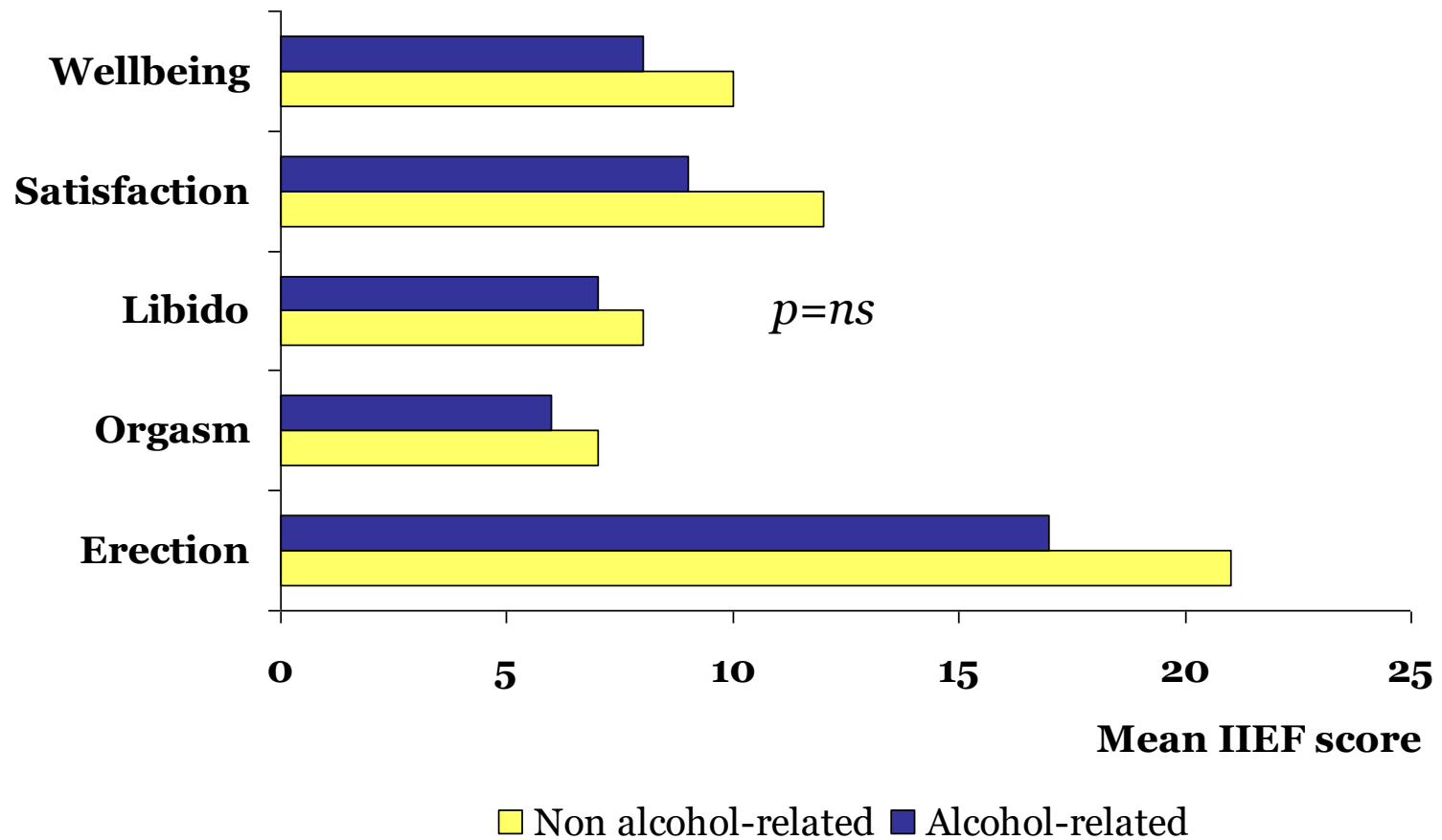




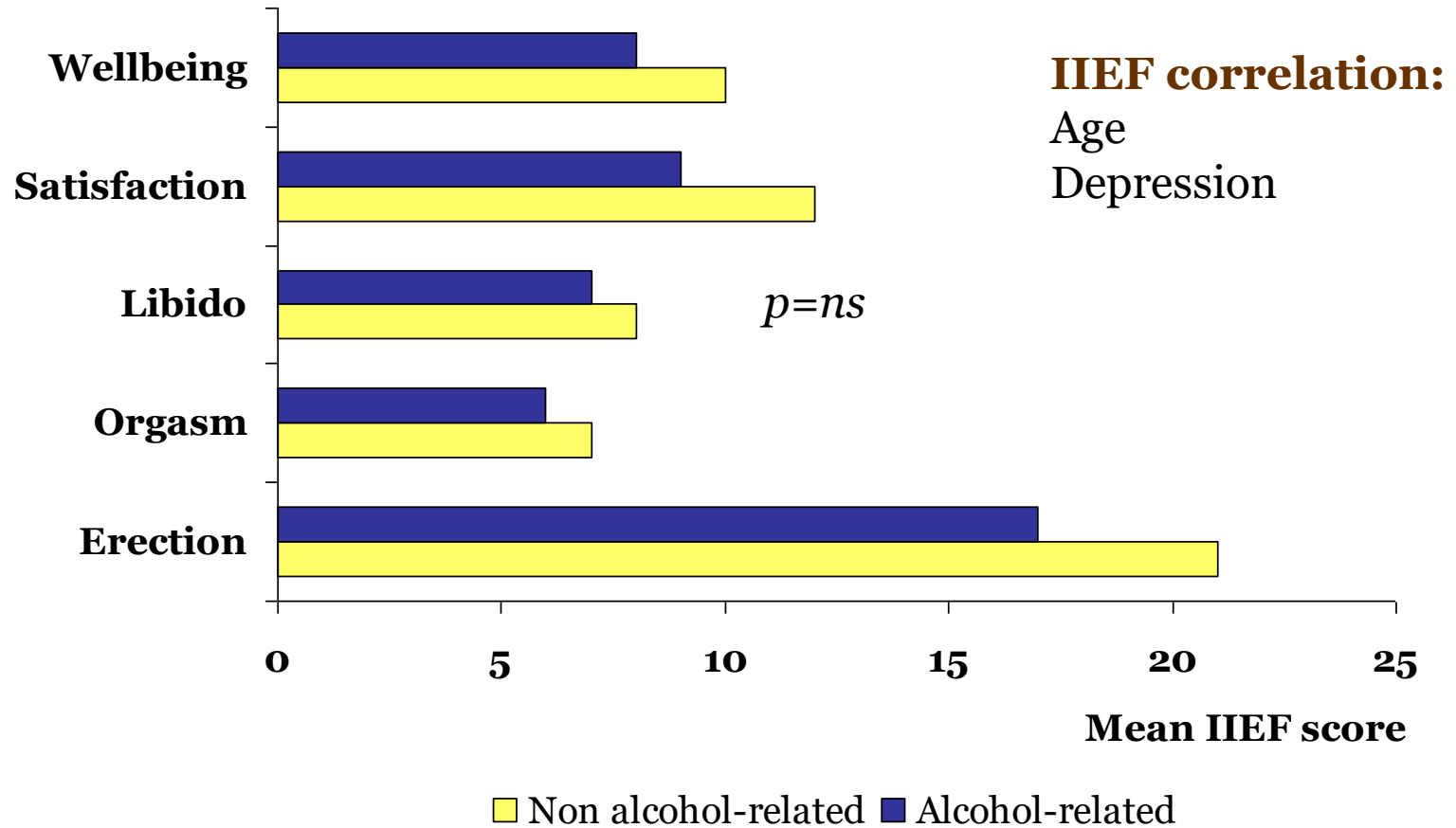
## Sexual dysfunction in 45 women with liver cirrhosis and 54 women after liver transplantation



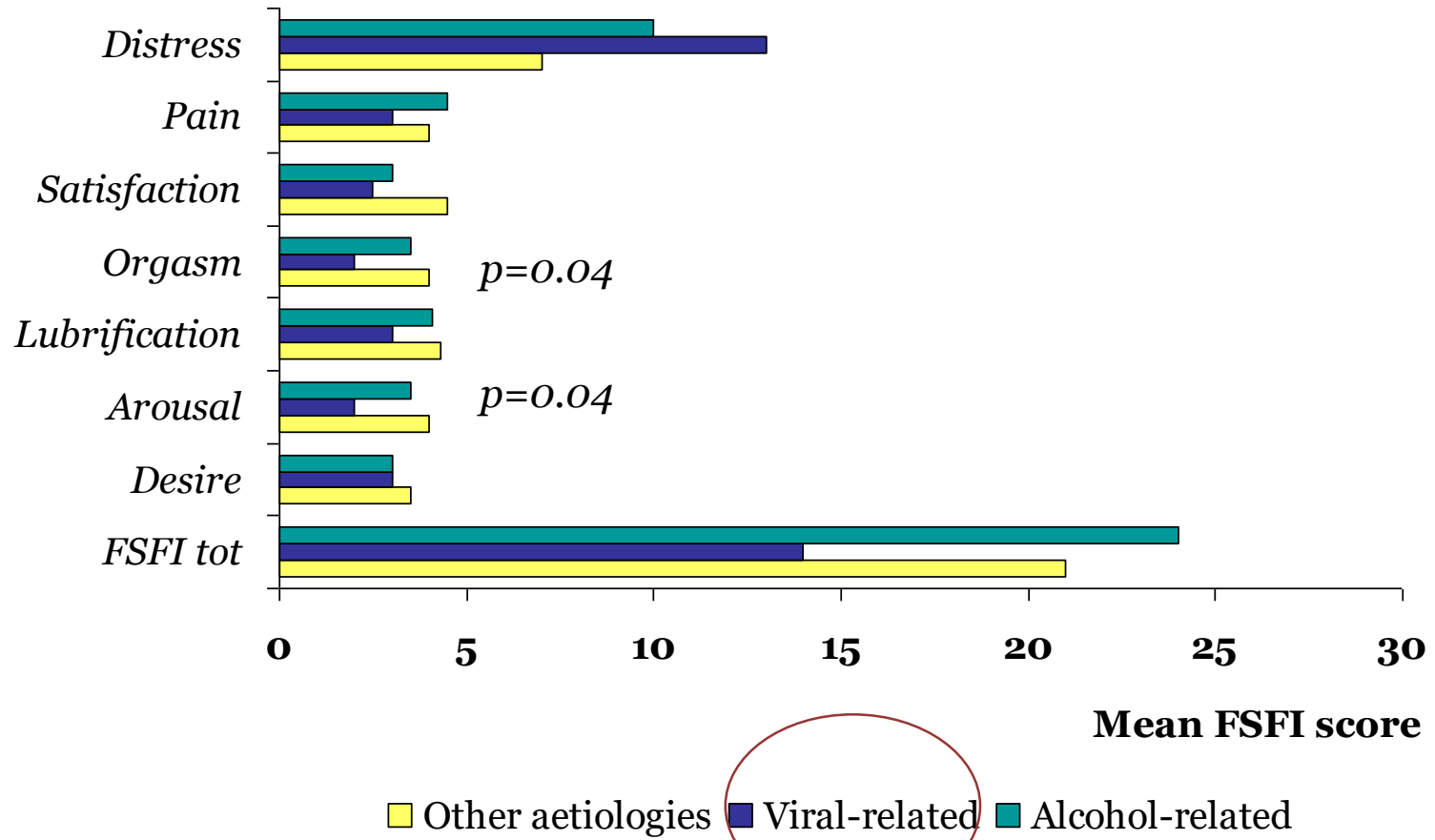
# Mean International Index Erectile Function (IIEF) score in 123 male patients transplanted for alcohol- and non alcohol-related liver disease



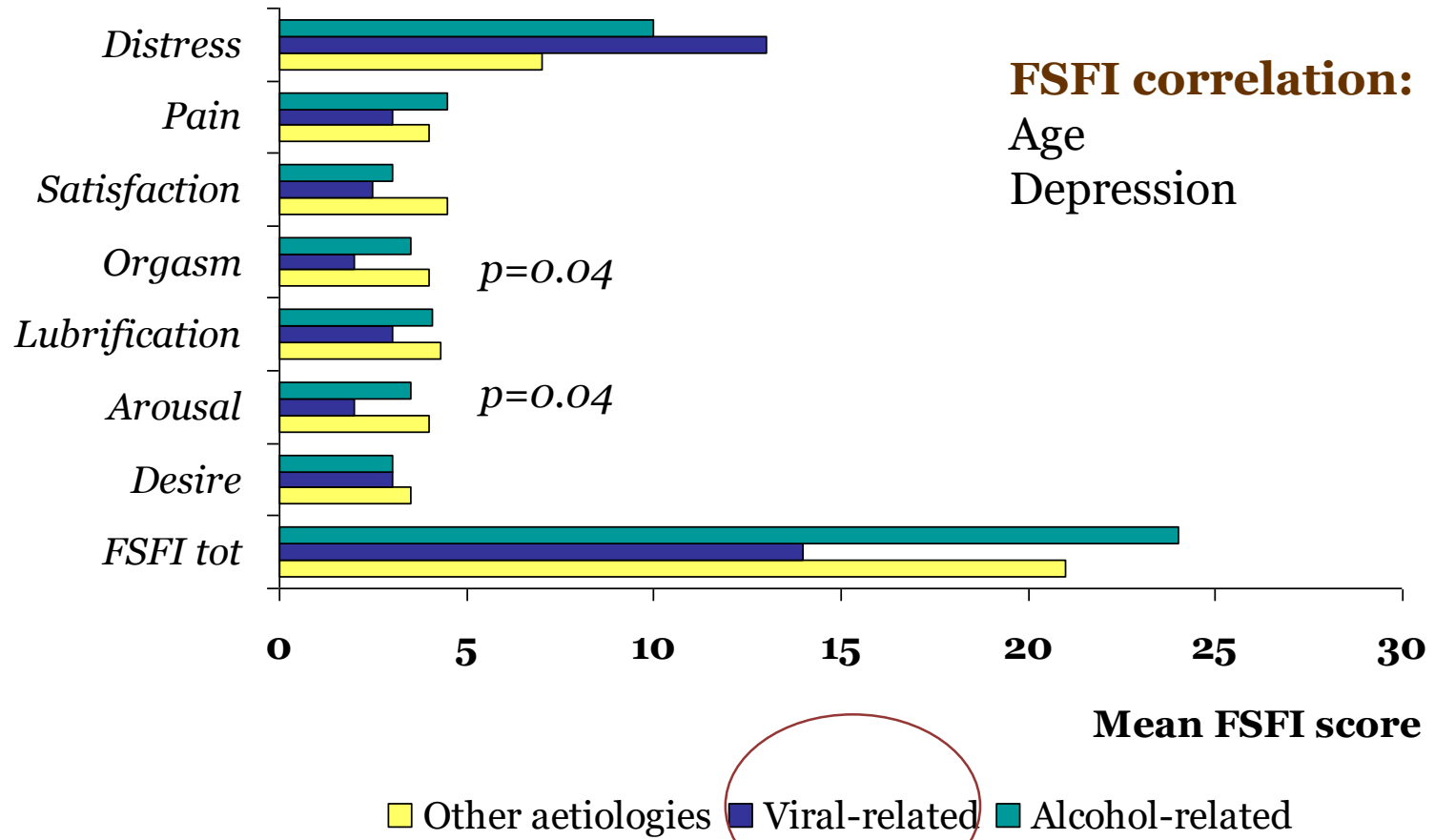
# Mean International Index Erectile Function (IIEF) score in 123 male patients transplanted for alcohol- and non alcohol-related liver disease



# Mean Female Sexual Function Index (FSFI) score in 54 liver transplanted female patients



# Mean Female Sexual Function Index (FSFI) score in 54 liver transplanted female patients

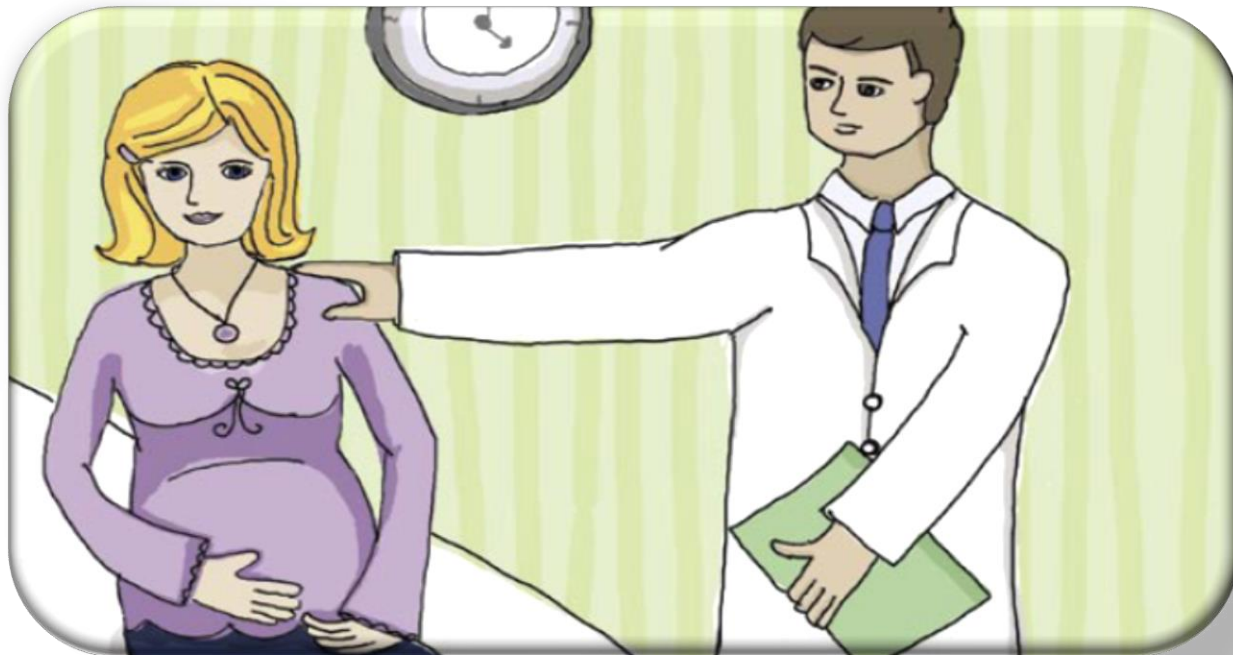


Burra & Villa

AISF Position Paper

## ***Liver transplantation and pregnancy***

Digestive and Liver Disease 2016



**Table 4. FDA Categories of Immunosuppressive Medications Commonly Used in Transplantation.**

Type of Therapy*	FDA Category†
<b>Induction</b>	
Muromonab-CD3 (Orthoclone OKT3)	C
Daclizumab (Zenapax)	C
Basiliximab (Simulect)	B
Antithymocyte globulin (Thymoglobulin)	C
Antithymocyte globulin, antilymphocyte globulin (ATGAM, ATG)	C
<b>Maintenance</b>	
Calcineurin inhibitors	
Cyclosporine (Neoral, Sandimmune, Gengraf)	C
Tacrolimus (Prograf)	C
Antiproliferative agents	
Mycophenolate mofetil (CellCept, Myfortic)	C
Azathioprine (Imuran)	D
Sirolimus (formerly called rapamycin; Rapamune)	C
Corticosteroids	
Prednisone	B
<b>Treatment of rejection</b>	
Methylprednisolone	C
Muromonab-CD3 (Orthoclone OKT3)	C
Antithymocyte globulin (Thymoglobulin)	C
Antithymocyte globulin, antilymphocyte globulin (ATGAM, ATG)	C

A = no risk in human studies

B = no evidence of risk in humans has been found

C = human risk cannot be ruled out

D = evidence of human risk

X = contraindicated

## mTORi and fertility in men

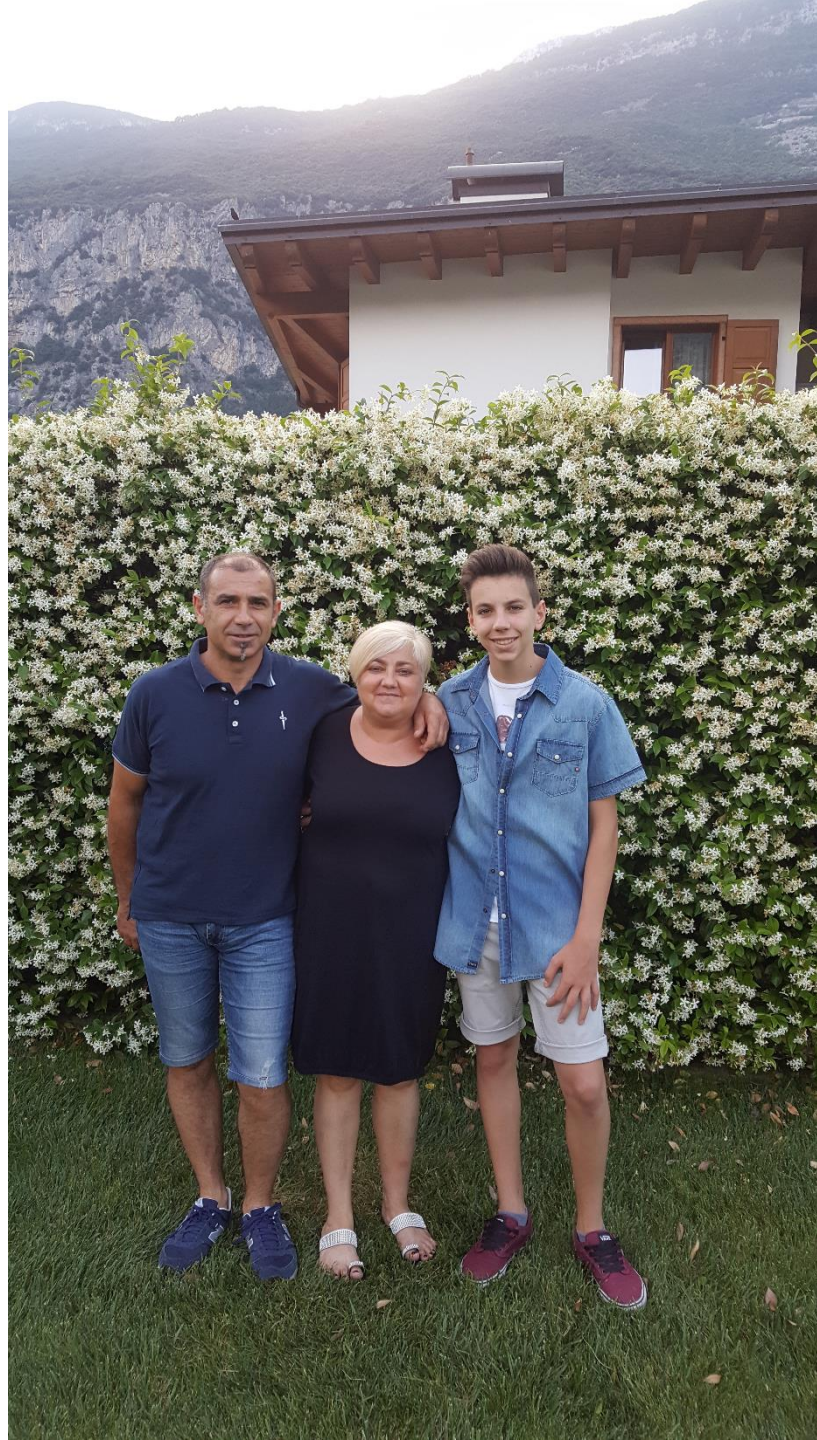
- Sirolimus and Everolimus treatment results in a decrease in testosterone level and increase in LH and FSH.
- Spermatogenesis seems to be disrupted.
- They have deleterious actions on the testis and impairs gonadal function after transplantation.



# Successful pregnancy in a liver transplant recipient treated with cyclosporine and azathioprine

*Loreno M & Burra P, Transpl Int 2005;17:730-734*

- 33-year-old woman, liver transplantation for Caroli's disease, on cyclosporine and azathioprine.
- 2 years later *de novo* HBV hepatitis, on lamivudine.
- 4 years later the patient became pregnant (lamivudine, cyclosporine and azathioprine were not discontinued).
- The course of gestation was uneventful, caesarean section after 36 weeks, the newborn infant was a healthy male weighing 3.080 g and measuring 50 cm.



# Risk of pregnancy complications in the recipient

- Hypertension (20-40%)
- Pre-eclampsia (10-30%)
- Diabetes (10%)

# Pregnancy outcome in liver recipients on neoral vs. tacrolimus

*Sifontis NM, Am J Transpl 2007;S2:1264A*

	<b>Neoral</b>	<b>Tacrolimus</b>
Recipients	22	42
Pregnancy outcomes	36	59
Livebirths	30	42
Spontaneous abortions	6	16
Stillbirths	0	1
Gestational age, mean±SD (wk)	37.4±2.8	36.4±3.4
Birth weight, mean±SD (g)	2750±750	2684±782
Maternal comorbid pregnancy (%)		
Hypertension*	<b>44</b>	<b>21</b>
Diabetes*	<b>0</b>	<b>12</b>
Preeclampsia	27	17
Rejection	3	7
Post-partum rejection	3	15

\*p<0.05

# Breastfeeding and Immunosuppressive Drugs

- The exposure to immunosuppressants via breast milk is smaller than during the pregnancy.
- Only 0.1% of a **Steroid** dose passes to breast milk.
- In some studies, no detrimental effects of **Azathioprine** on the newborns have been proven.
- **Mofetil Mycophenolate** due to its confirmed teratogenic there are no studies describing its activity during breastfeeding in humans. Studies on rats have shown that it passes to the mother's milk.

Greenberger Clin Pharmacol Ther 1993;53:324-328.

Ito Am J Obstet Gynecol 1993;168:1393-1399.

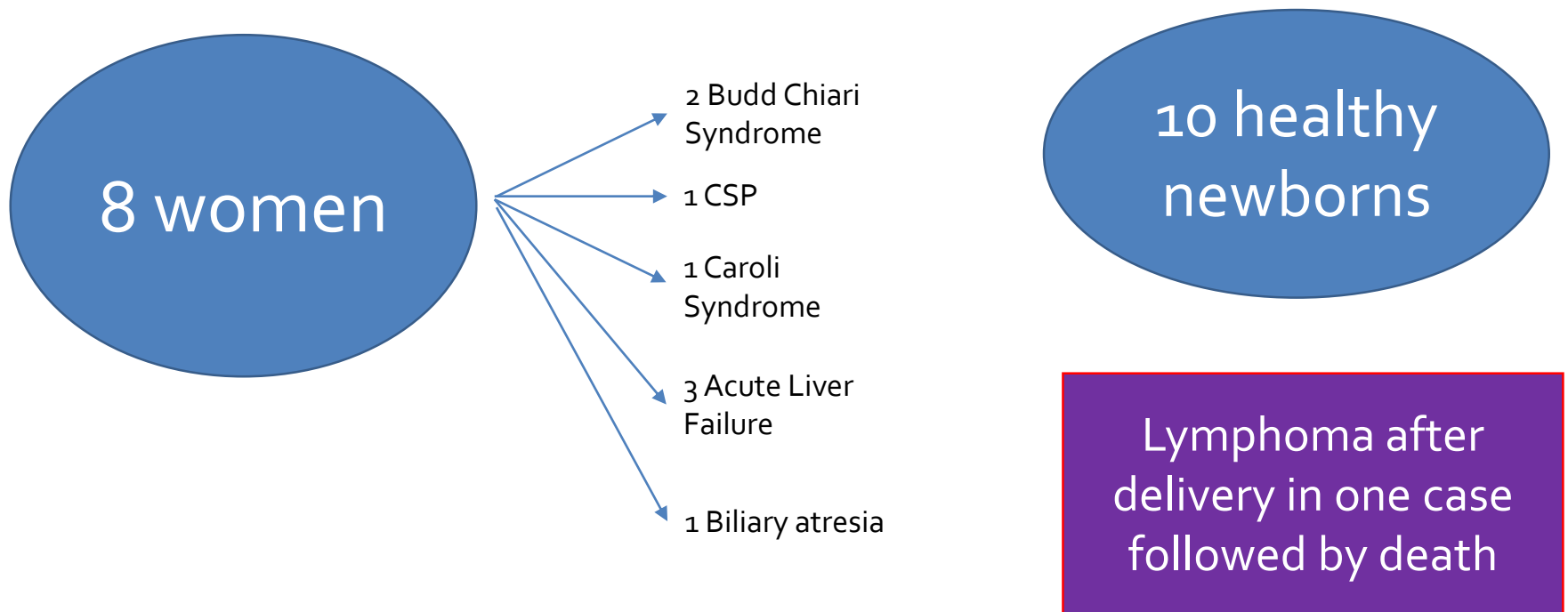
Saarikoski Am J Obstet Gynecol 1973;115:1100-1106.

Mycophenolate REMS. Safety information. <https://www.mycophenolaterems.com/SafetyInformation.aspx>. Accessed May 26, 2016.

# Contraceptive methods available after liver transplantation

	Effectiveness	Drug interactions	Reversibility
<b>IUD (Intrauterine contraceptive devices)</b>	++	-	++
<b>COCs (Combined oral or transdermal contraceptives)</b>	++	+	++
<b>Progestin-only pill</b>	++	(-)	++
<b>DMPA (Depot medroxy-progesterone acetate (every 3 months injection))</b>	++	(-)	++
<b>Barrier method</b>	+	-	++
<b>Surgical sterilization</b>	++	-	-

# Pregnancy after liver transplantation: Padua Experience 1990-2020



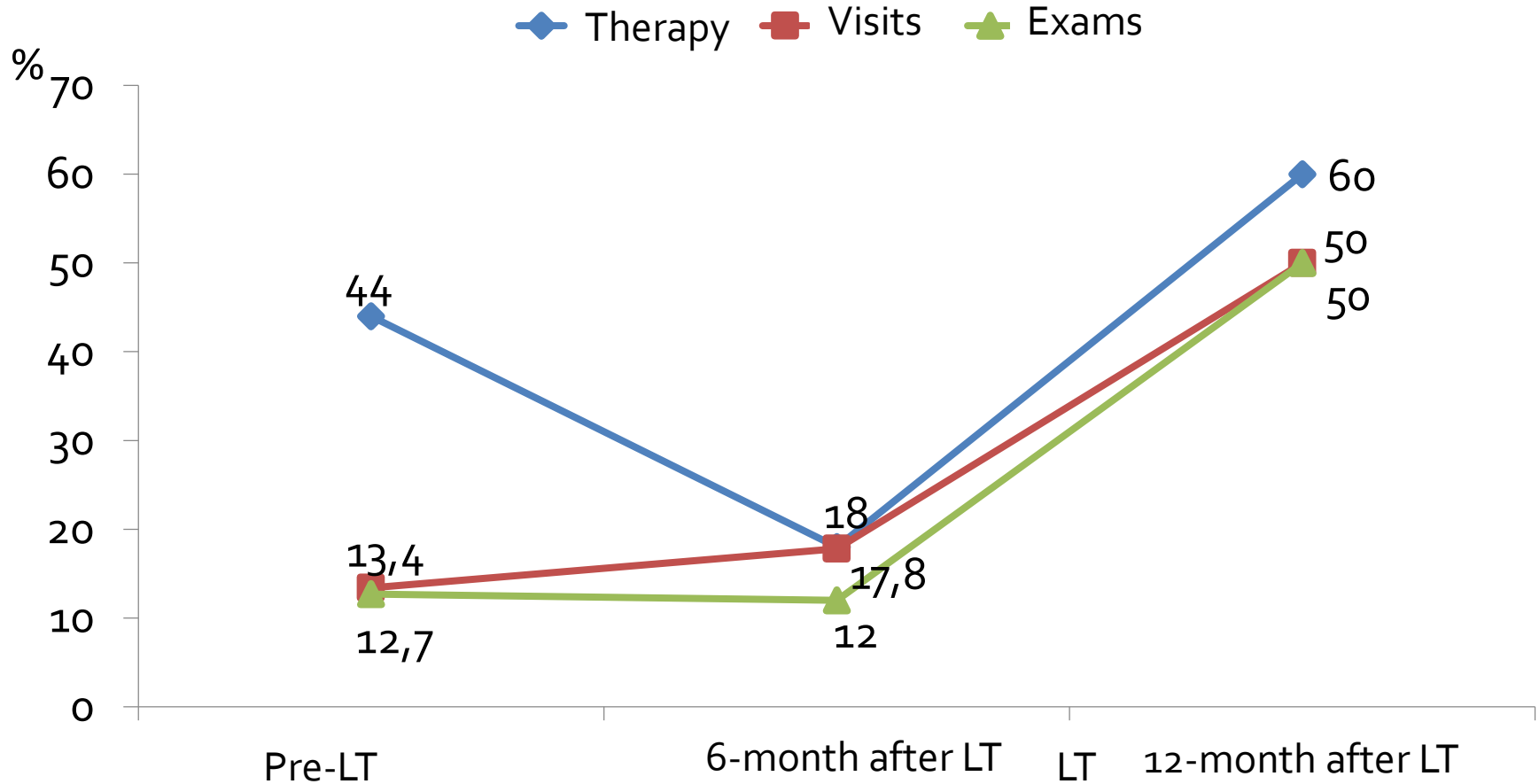






# Non-adherence to medical prescriptions before and after liver transplantation (LT)

*No difference according to gender*



## Adherence in 218 solid organ transplant recipients

- Anonymous 15-item questionnaire, assessing adherence to immunosuppression, lifestyle, and general prescriptions.
- The percentage of nonadherent kidney transplant recipients was significantly lower compared with other organ transplanted patients.
- Among patients nonadherent to the correct lifestyle, **the rates of men** and of patients with **disability pension** were significantly higher compared to adherent patients.

# Conclusion

*«In the liver transplant setting, the notion of gender as a binary female/male factor is now giving way to the awareness of more complex processes within the female gender that follow also hormonal patterns and need to be addressed directly and specifically.»*

P.Burra, E.De Martin, S.Gitto, E.Villa  
on behalf of WIH  
Liver Transplantation 2013

