



LA SALUTE COME DIMENSIONE DI BENESSERE: UNA
PROSPETTIVA DI GENERE

IL TRAPIANTO COME PARADIGMA DELLA DISEGUAGLIANZA NELLE CURE

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- Liver transplantation as a life-saving therapy
- Who can have access to this therapy?
- How does the current allocation system favor male gender?
- What are the complications that affect women after liver transplantation?



OUTLINE

- Gender and End-Stage Liver Disease
- Gender and mortality on the waiting for liver transplantation
- Allocation – Prioritization
- Outcome after liver transplantation



LIVER TRANSPLANTATION IS A LIFE-SAVING THERAPEUTIC STRATEGY

- Mortality without liver transplant
 - ESLD
 - 1-yr survival for Child's A, B, C is approximately 100%, 80%, and 45%, respectively.
 - Acute liver failure (50-80%)
 - HCC (mean survival of 6-20 months)
 - Other conditions

LIVER TRANSPLANTATION IS A LIFE-SAVING THERAPEUTIC STRATEGY



Table 1 Mortality at 3 months in patients hospitalized with liver disease stratified according to MELD score

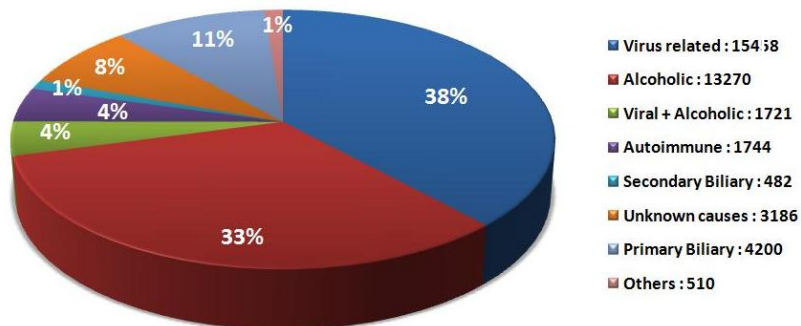
MELD score	Three-month mortality in hospitalized patients (%)
≥40	100
30-39	83
20-29	76
10-19	27
<10	4

Kamath, Hepatology 2001.



European Liver Transplant Registry

Primary indications of Liver Transplantation in 40571 Cirrhosis in Europe 01/1988 - 06/2008





Centro Nazionale Trapianti

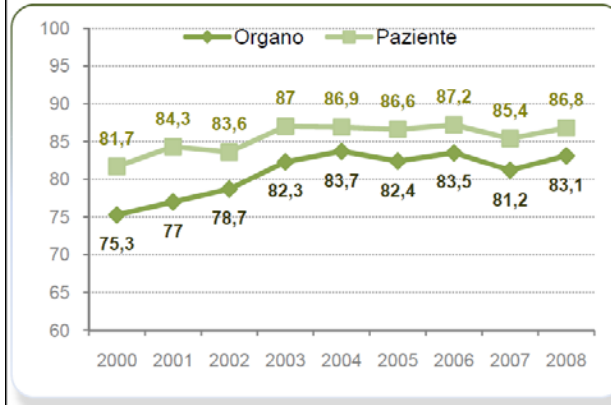


Rete Nazionale Trapianti

ONE-YEAR SURVIVAL AFTER LT



Sopravvivenza Adulti Organo e Paziente ad un anno



THE PROPORTION OF MALE PATIENTS ON THE WAITING LIST IS GREATER



TABLE 1. Demographic and Clinical Characteristics of the Patients (n = 8566)

Characteristic	Data
Age at listing (mean \pm SD in years)	51.9 \pm 9.4
Gender	
Male	5775 (67.4%)
Female	2791 (32.6%)
Race*	
White	6571 (76.9%)
Black	663 (7.8%)
Asian	228 (2.7%)
Other	1085 (12.7%)
Underlying Liver Disease	
HCV	3943 (46.0%)
ALD	2720 (31.8%)
NAFLD/NASH	1186 (13.9%)
PSC	560 (6.5%)
HBV	548 (6.4%)
PBC	435 (5.1%)
AIH	332 (3.9%)
A1AT	157 (1.8%)
Hemochromatosis	111 (1.3%)
Other liver disease [†]	404 (4.7%)
Diabetes mellitus	1752 (20.5%)
Initial calculated MELD at listing [median (Q1-Q3)]*	17 (13-22)
Days on waiting list [median (Q1-Q3)]*	62 (17-173)



Brady, Liver Transpl 2008

IN AN ERA OF ORGAN SHORTAGE,
WHO GETS THE LIVER?



?

ORGAN ALLOCATION



- MELD and non-MELD
- Regional basis
- Center basis
- Donor-recipient match according to blood group, HCV status, donor age, organ size

WAITING TIME IS GREATER FOR FEMALE PATIENTS



- Baltimore: 7422 entries to the waiting list
- Factors influencing waiting time and successful receipt of cadaveric LT
- **Women**, Hispanic-Americans and Asian-Americans waited longer for a transplant
- The risk of dying before LT was greater for critically ill and repeat transplant patients, **women**, older patients, Asian-Americans and African-Americans

Klassen, Med Care, 1998

HEPATOLOGY

Risk factors for liver transplantation waiting list mortality

Michael A Fink,^{*1} S Roger Berry,^{*1} Paul J Gow,^{*} Peter W Angus,^{*} Bao-Zhong Wang,^{*1} Vijayaragavan Muralidharan,^{*1} Christopher Christophi^{*1} and Robert M Jones^{*1}

^{*}Liver Transplant Unit Victoria, and ¹Department of Surgery, The University of Melbourne, Austin Hospital, Melbourne, Victoria, Australia

- The mean annual WL mortality was 10.2% for adult patients
- Factors associated with WL death included **female sex**, fulminant hepatic failure, primary non-function, blood group O, MELD ≥ 20 .

Fink, J Gastroenterol Hepatol, 2007.



Sex-Based Disparities in Liver Transplant Rates in the United States

- Access to LT:
 - Pre-MELD era females had a significant 9% ($p < .0001$) lower transplant rate compared to males
 - In the MELD era, disparity increased to 14% ($p < .0001$).
 - MELD <15 no significantly different transplant rates than males,
 - MELD 20-29: transplant rates 20% lower for females
 - MELD 30-40: females had 12% lower transplant rate

Mathur, Am J of Transpl 2011



Sex-Based Disparities in Liver Transplant Rates in the United States

- ***Geographic variation in sex-based disparities in liver transplant rates.***
- Females have significantly lower transplant rates in 6 of the 11 OPTN regions, with a maximum deficit of 35% in the Pacific Northwest.

Mathur, Am J of Transpl 2011

MELD ALLOCATION SYSTEM FOR LT PRESENTS A DISADVANTAGE FOR WOMEN



- MELD includes creatinine, which is typically lower in females
- A total of 40,393 patients from UNOS database
- Compared with men, women had lower median serum creatinine (0.9 vs. 1.0 mg/dl), eGFR (72 vs. 83 ml/min/1.73 m²), and mean MELD (16.5 vs. 17.2; all p < 0.0005), but within most MELD strata, had higher bilirubin and INR.
- After adjusting for relevant covariates including creatinine and body weight, women were less likely than men to receive a LT (hazard ratio [HR] 0.85; 95% CI 0.79-0.87) and had greater 3-month mortality (HR 1.13; 95% CI 1.05-1.21).

Myers, J Hepatol , 2011.

MELD ALLOCATION SYSTEM FOR LT PRESENTS A DISADVANTAGE FOR WOMEN



- Revision of MELD and MELDNa to include eGFR did not improve discrimination for 3-month mortality.
- Women are disadvantaged under MELD potentially due to its inclusion of creatinine. However, since including eGFR in MELD does not improve mortality prediction, alternative refinements are necessary.

Myers, J Hepatol , 2011.

ALLOCATION SYSTEM – ANATOMICAL DISADVANTAGE



- Although a strict male-male female-female allocation is not mandatory, organ size is a variable taken into consideration for organ allocation.
- Female recipients compete against pediatric donors for smaller livers.

SHOULD DONORS AND RECIPIENTS BE MATCHED IN LIVER TRANSPLANTATION?



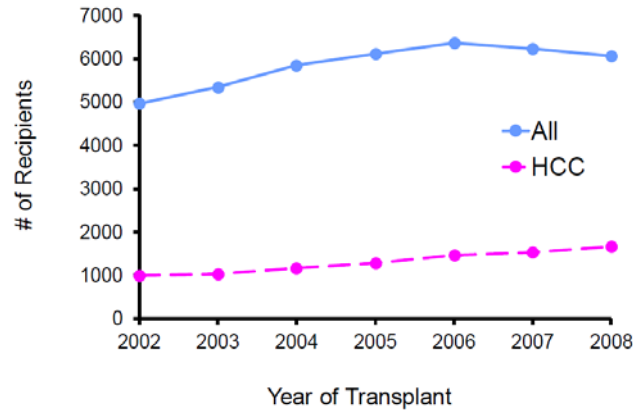
Table 2

Requirements for an organ allocation system with donor and recipient matching

- (1) Adherence to the sickest-first policy, while limiting the risk of futility.
- (2) The lowest acceptable post-transplant survival benefit should be defined and agreed upon (avoidance of futility).
- (3) Identification of all donor factors which are associated with worse outcome.
- (4) Consensus on the definition of “expanded criteria donors”.
- (5) Identification of combinations of donor and recipient profiles which have an impact on outcome.
- (6) Variables identified under (3) and (4) should be objective and available at the time of organ offer.
- (7) Not only severity of liver disease, but also specific etiologies should be considered.
- (8) Development of a new allocation model which includes all the above-mentioned principles and knowledge.
- (9) Continuous re-evaluation and validation after the allocation system has come into practice.



Figure IV-3: Comparison of HCC Liver Recipients to All Liver Recipients by Year of Transplant



Source: SRTR Analysis, Data as of May 2009.

•Male:female ratio of HCC ranges from 2:1 to 4:1

RISK OF DE NOVO HCC ON WL FOR LT



TABLE 2. Bivariate Analysis of Predictors of De Novo HCC in Patients Awaiting Orthotopic Liver Transplantation

Variable	HCC Present (n = 1167)	HCC Not Present (n = 7399)	Unadjusted Odds Ratio	95% Confidence Interval	P Value
Age at listing (mean ± SD)	54.9 ± 8.0	51.4 ± 9.6	1.04	1.04, 1.05	<0.0001
Sex			Reference		
Female	254 (21.8%)	2537 (34.3%)			
Male	913 (78.2%)	4862 (65.7%)	1.88	1.62, 2.17	<0.0001
Race			Reference		
White	855 (73.3%)	5716 (77.3%)			<0.0001
Black	84 (7.2%)	579 (7.9%)	0.97	0.76, 1.23	0.8028
Asian	58 (5.0%)	170 (2.3%)	2.28	1.68, 3.10	<0.0001
Other	170 (14.6%)	915 (12.4%)	1.24	1.04, 1.49	0.0175
Underlying liver disease					
HCV	797 (68.3%)	3146 (42.5%)	2.91	2.55, 3.32	<0.0001
ALD	367 (31.5%)	2353 (31.8%)	0.98	0.86, 1.12	0.8099
NAFLD/NASH	104 (8.9%)	1082 (14.6%)	0.57	0.46, 0.71	<0.0001
PSC	16 (1.4%)	544 (7.4%)	0.18	0.11, 0.29	<0.0001
HBV	110 (9.4%)	438 (5.9%)	1.65	1.33, 2.06	<0.0001
PBC	23 (2.0%)	412 (5.6%)	0.34	0.22, 0.52	<0.0001
AIH	16 (1.4%)	316 (4.3%)	0.31	0.19, 0.52	<0.0001
AIAT	14 (1.2%)	143 (1.9%)	0.62	0.36, 1.07	0.0857
Hemochromatosis	10 (0.9%)	101 (1.4%)	0.63	0.33, 1.20	0.1575
Other liver disease*	16 (1.4%)	388 (5.2%)	0.25	0.15, 0.42	<0.0001
Diabetes mellitus	283 (24.3%)	1469 (19.9%)	1.29	1.12, 1.50	0.0006
Initial calculated MELD at listing [median (Q1-Q3)]	13 (10-16)	17 (14-23)	0.87	0.86, 0.88	<0.0001
Days on waiting list [median (Q1-Q3)]	68 (23-207)	61 (16-168)	1.001	1.00, 1.001	<0.0001

Brady, Liver Transpl 2008

HEPATITIS C VIRUS INFECTED FEMALES HAVE A HIGHER RISK OF ADVANCED FIBROSIS AND GRAFT LOSS AFTER LIVER TRANSPLANTATION THAN MALES



1264 patients transplanted for HCV

Median follow-up 3 years

24% were female

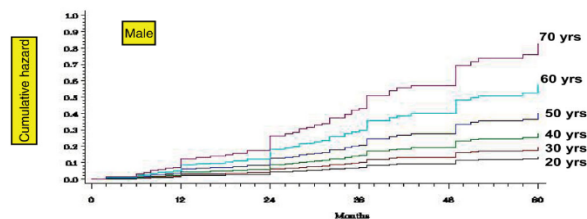
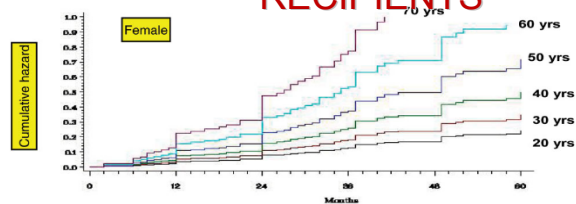
Biopsy proven bridging fibrosis or cirrhosis



**FEMALE GENDER INDEPENDENT PREDICTOR
OF ADVANCED RECURRENT DISEASE
(HR 1.31, 95% CI, 1.02-1.70, P=0.04)**

Lai, Hepatology 2011

INCREASED SEVERITY OF HCV RECURRENT DISEASE IN FEMALE RECIPIENTS

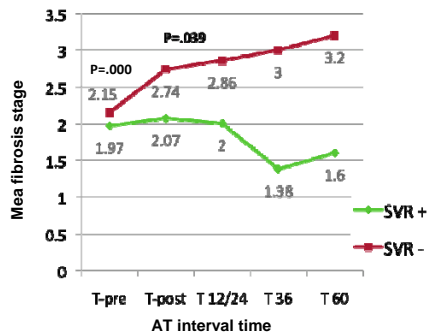


Cumulative hazard of severe fibrosis after LT in female (top) and in male (bottom) recipients, by donor age.

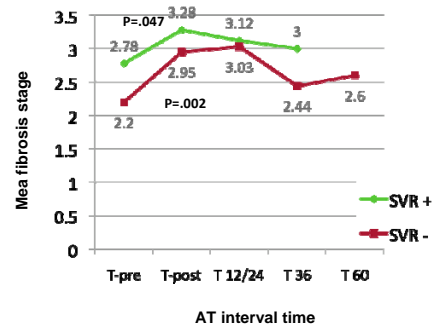
Belli, Liver Transpl 2007

FIBROSIS PROGRESSION: SVR+ VS SVR-

Male



Female



De Martin, AISF 2010

CONCLUSION



- There is a need to consider gender in models of severity of liver disease.
- Score to give priority in the waiting list for liver transplantation needs to be revised according to data on gender.
- HCV recurrence after liver transplant is more aggressive in female patients; therefore a different therapeutic approach is mandatory.

