

When is a Patient Too Sick for Liver Transplantation?

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CUTTING EDGE of **TRANSPLANTATION**

TRANSPLANT SUMMIT 2019

***NO SIZE FITS ALL:** Uncovering the
Potential of Personalized Transplantation*

Disclosure

Research: Gilead, Novartis, Allergan, Conatus

Advisory Boards: Gilead, Pfizer, Merck

Speaking: HCV Viewpoint, Simply Speaking

Board Participation: CLDF

Learning Objectives

To review the general indications and contraindications for liver transplantation

To outline the challenges with determining when a patient is “too sick” for transplant

To discuss possible strategies to determine a consistent approach in patient selection in the extremes

When is a Patient Too Sick for Liver Transplant?

- We all agree these patients exist
- We can't agree on a definition
- When limited answers exist (and you've been given 15 minutes)
- Frame the issue

“One man's meat
Is another man's
Poison”

Minimal Listing Criteria

Minimal Criteria for Placement of Adults on the Liver Transplant Waiting List: A Report of a National Conference Organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases

Michael R. Lucey, Kimberly A. Brown, Gregory T. Everson, John J. Fung, Robert Gish, Emmet B. Keeffe, Norman M. Kneteman, John R. Lake, Paul Martin, Sue V. McDiarmid, Jorge Rakela, Mitchell L. Shiffman, Samuel K. So, and Russell H. Wiesner



Liver Transplantation and Surgery, Vol 3, No 6 (November), 1997: pp628-63

Contraindications to Liver Transplant

Absolute

- Advanced cardiopulmonary disease
- Uncontrolled Sepsis
- Malignancy outside the liver →
- PVT →
- Liver cancer →
- Active substance use →
- HIV →
- Advanced age →
- Organ failure outside the liver →

Relative

- Poor compliance
- Poor functional status
- Limited social support

Definition of “Too Sick”

- Medically? Surgically? Functionally? Socially? Economically?
- Patients who are not deemed candidates may end up in this category
- Little consensus both on when not to list as well as when to remove from the list
- Varies by patient, provider and program

???Maximal Listing Criteria

Summary report of a national conference: Evolving concepts in liver allocation in the MELD and PELD era

Oltoff KM, Brown RS, Delmonico RL, Freeman RB, McDiarmid SV, Merion RM, Millis JM, Roberts JP, Shaked A, Wiesner RH, Lucey ML

Liver Transplantation 2004: 10 (S10); A6-A22

Should There be Criteria for Delisting or Deactivation of Patients?

- Because patients likely deemed “too ill” for transplant are the most critically ill, the outcome without transplant in this group is likely exceedingly poor
- This any criteria for delisting need to be strongly evidence based, validated in the MELD allocation era, and biased in favor of transplantation

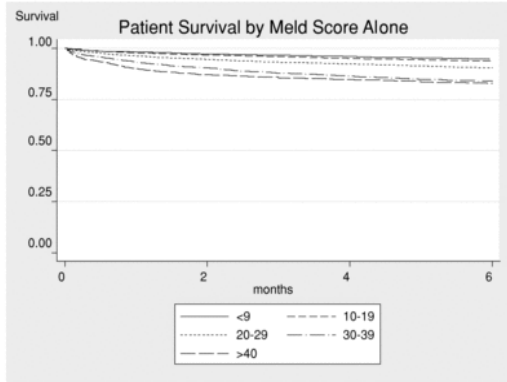
Survival
With Transplant



Survival
Without Transplant

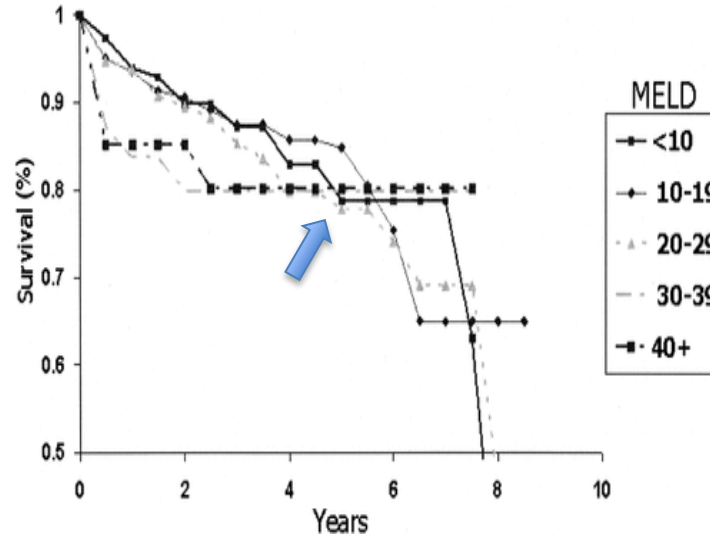
} Individual
Transplant
Benefit

Post Transplant Survival Based on MELD



Actuarial Survival for Liver Allograft Recipients Divided by MELD Score Categories				
Month	1	3	6	
MELD < 9	98%	97%	95%	
10-19	98%	96%	94%	
20-29	96%	93%	90%	
30-39	93%	88%	84%	
≥ 40	90%	85%	83%	

* All Groups p<0.05 compared to MELD < 9

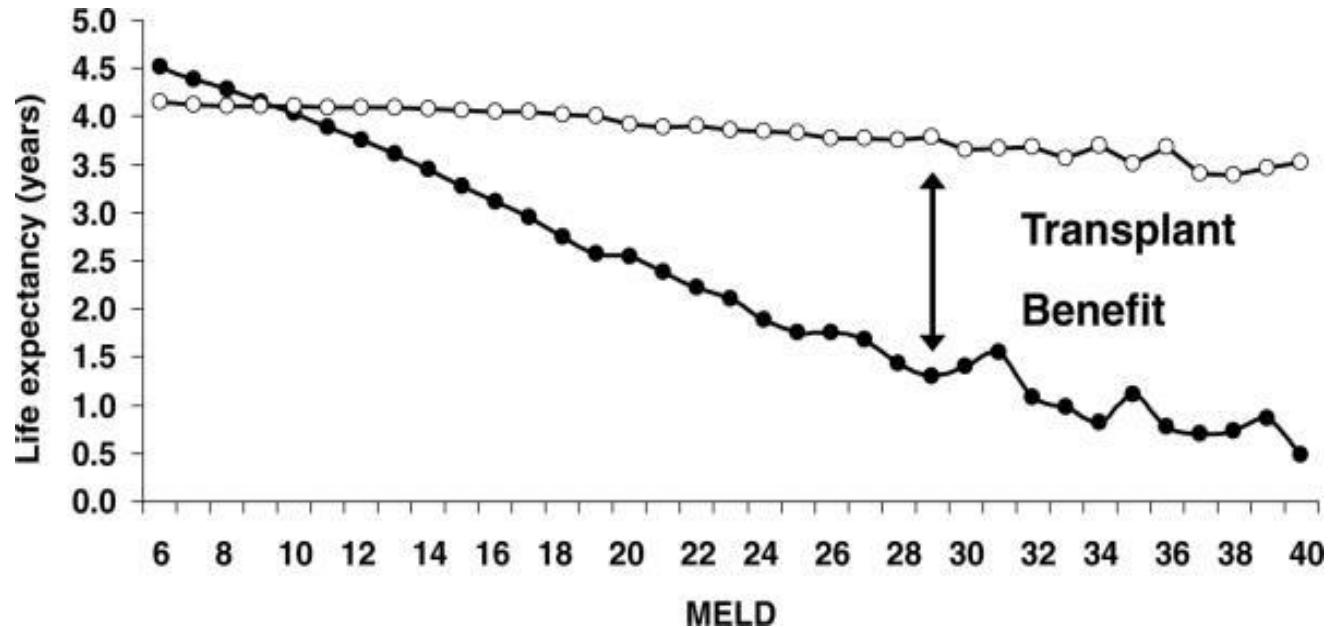


Desai NM, Transplantation 2004; 77: 99–106. Oltoff KM, Liver Transplantation: 10 (S10); A6-A22

Conclusion

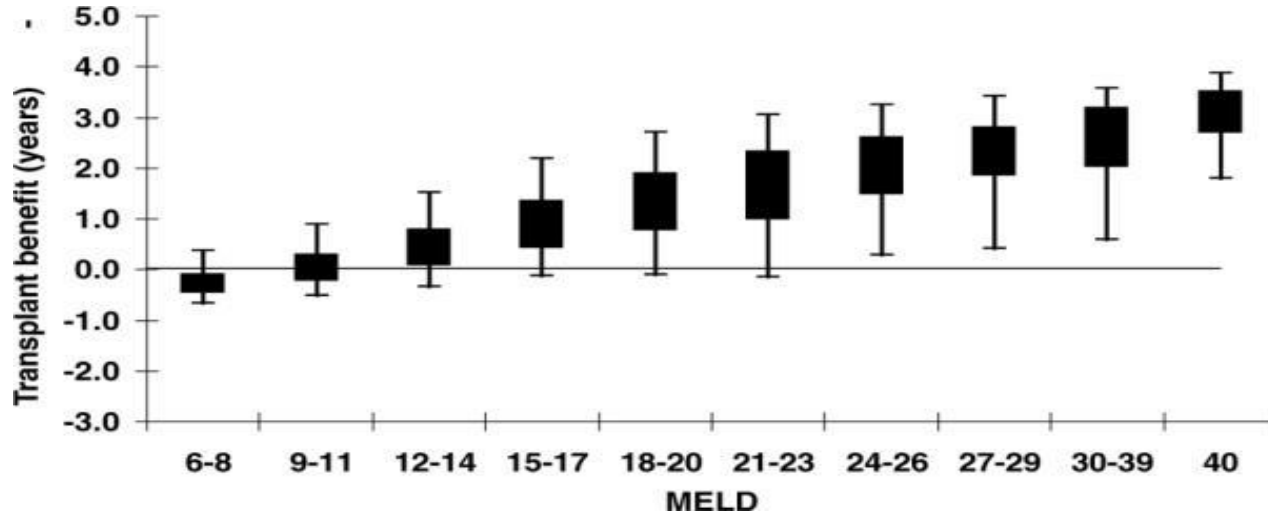
- An absolute minimum cutoff for acceptable predicted posttransplant survival is needed and endorsed by both the transplant community and society
- “It is likely that an expected survival rate below which transplant is not warranted would range from 40 to 60%”

Mean 5 Year Future Lifetime by MELD



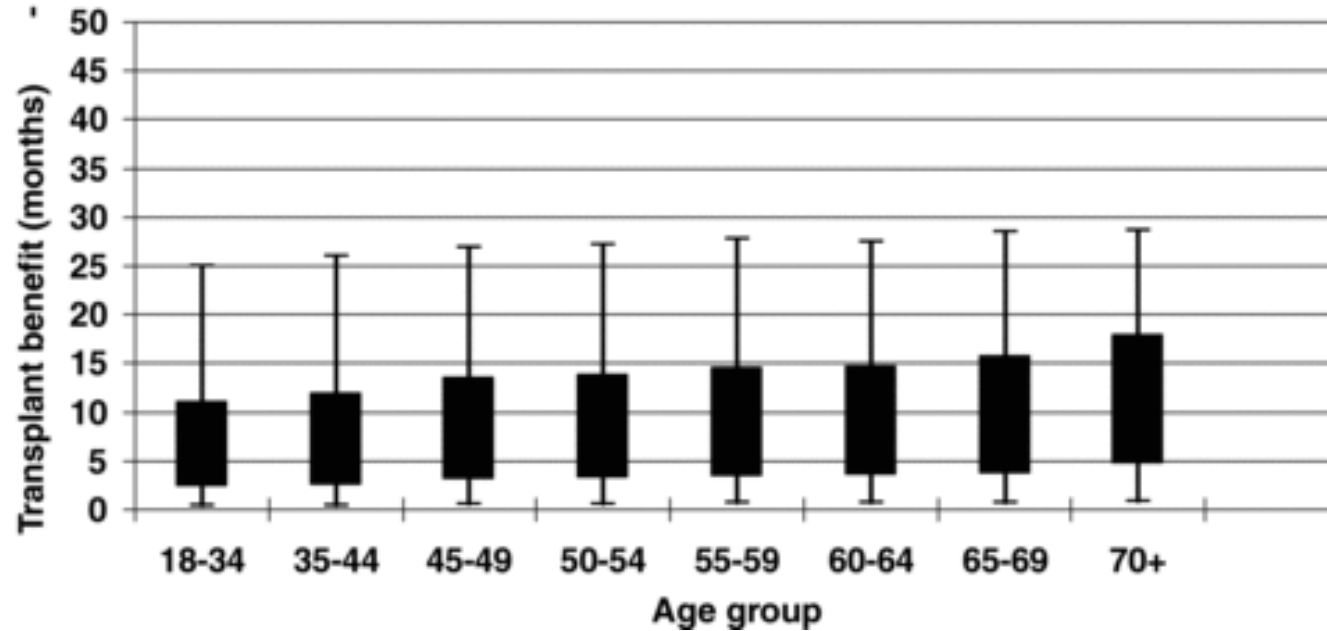
Schaubel DE. American J Transplant 2009; 9(4 Pt 2): 970-81

Benefit Score Distribution by MELD



Schaubel DE. American J Transplant 2009; 9(4 Pt 2): 970-81

Benefit Scores by Age Patients with Benefit > 0



Schaubel DE. American J Transplant 2009; 9(4 Pt 2): 970-81

What Can Change Over Time?

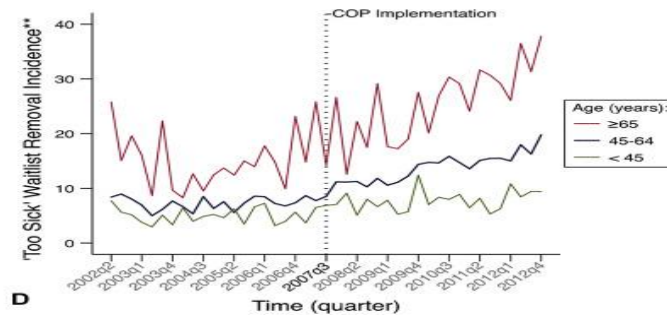
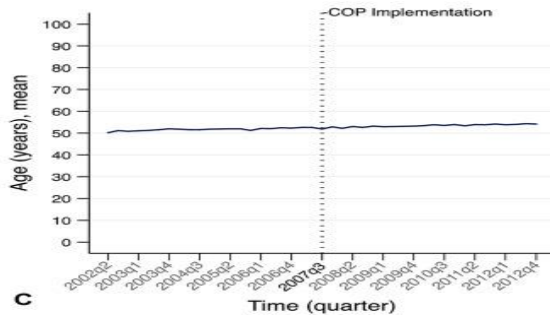
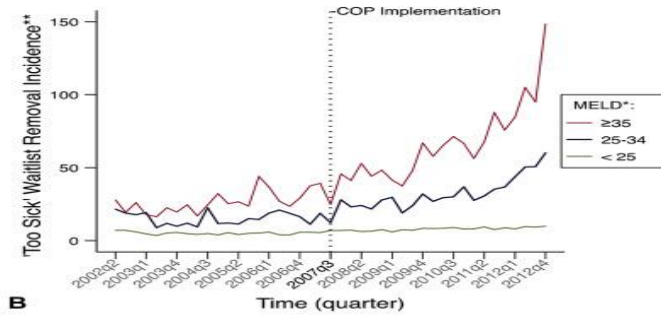
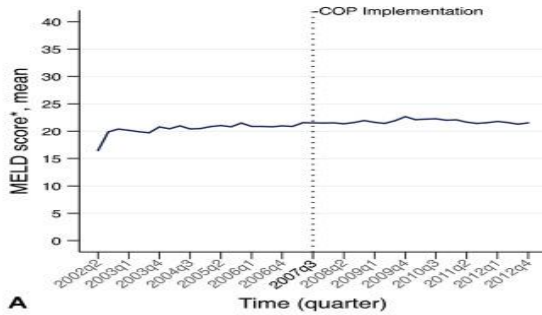
- Advancing Age
 - 25% of patients wait over 4 years on the list
 - Increased odds wait list mortality, decreased odds of transplant, increased odds of graft loss patients age 65 or over
- Sarcopenia and Frailty
 - Increased wait list mortality and hazard of death post transplant
- ACLF
- Worsening medical conditions
 - BMI > 35, CAD, DM, COPD, Chronic renal insufficiency

Malinis MF, Ann Transplant 2014;19:478-87, Tandon P, Liver Transpl 2012;18:1209-16, Englesbe MJ, J Am Coll Surg 2010;211:271-278, Moreau R, Gastroenterology 2013;144:1426-37, Gustot T, Hepatology 2015;62:243-252, Rana A, Am J Transplant 2008;8:2537-46, Tovikkai C, BMJ Open 2015;5:e006971-e16971, Volk ML, Liver Transpl 2007;13:1515-20

Risk of Non-Standard Criteria

- Selection (and hence opportunity) becomes variable
- Unintended bias is likely present
- Outside influence (CMS and contract expectations)

Influence of CMS



Dolgin NH, J Am College Surgeons 2016;222(6): 1054-65

Does 1 + 1 = 2 (or 3, or 4...)

NASH
DM

NASH
DM
BMI 42

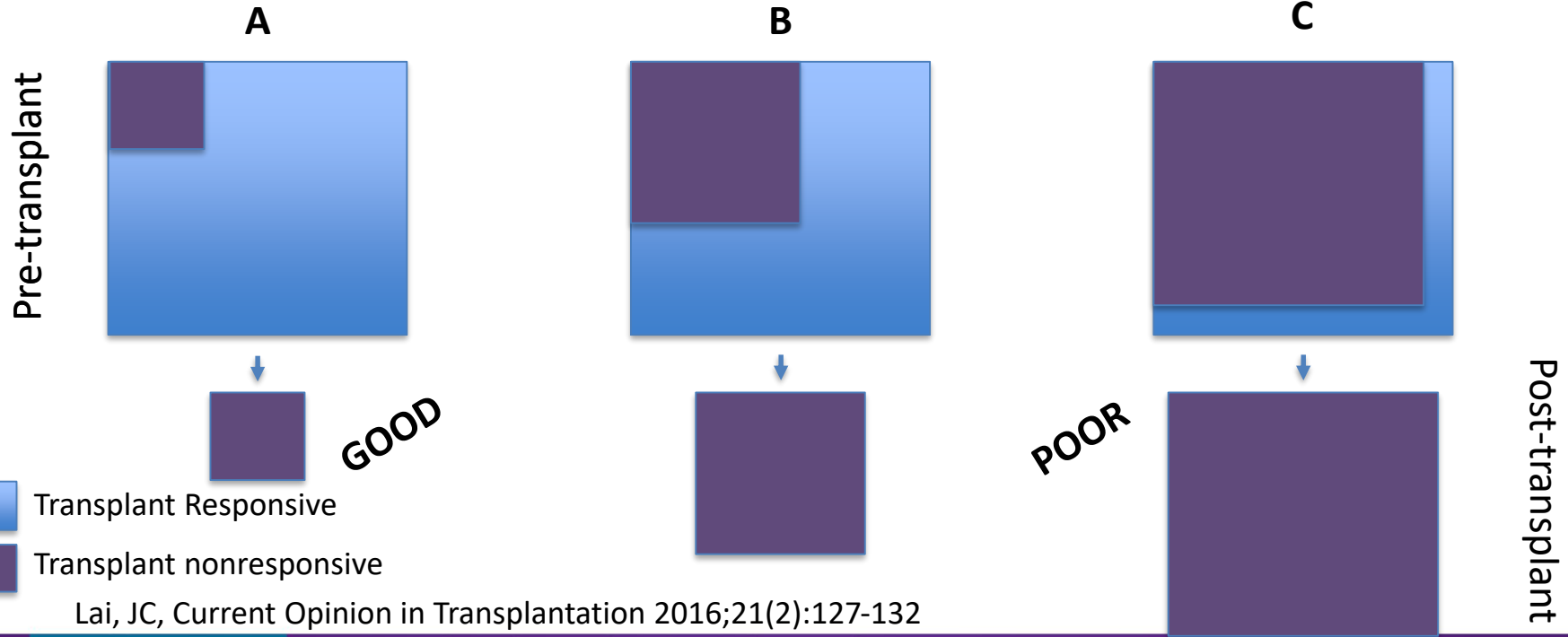
NASH
DM
BMI 42
GFR 47

NASH
DM
BMI 42
GFR 47
Cardiac Stent

NASH
DM
BMI 42
GFR 47
Cardiac Stent
Age 65

NASH
DM
BMI 42
GFR 47
Cardiac Stent
Age 65
Wheelchair

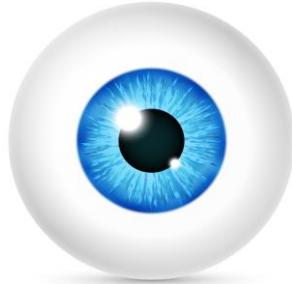
Framework for Evaluating Patients Deemed “Too Sick” (What Can We Fix With Transplant?)



Lai, JC, Current Opinion in Transplantation 2016;21(2):127-132

What are we left with?

- 1.

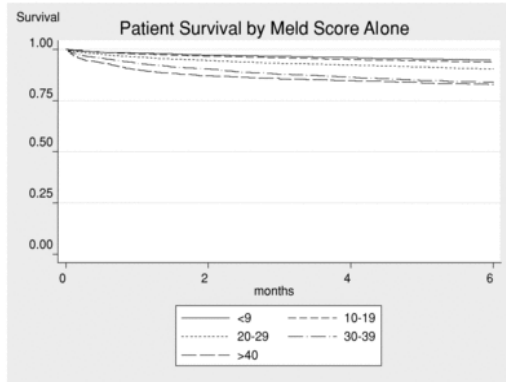


The Eyeball test

I have searched the Literature and find no supporting evidence For either

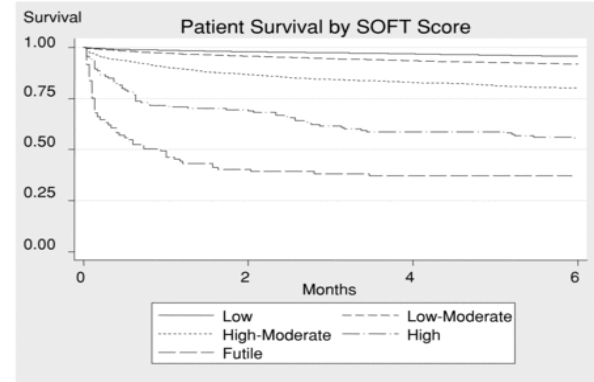
- 2. Pure as Caesar's Wife

Recipient Survival by SOFT Score



Month	1	3	6
MELD < 9	98%	97%	95%
10-19	98%	96%	94%
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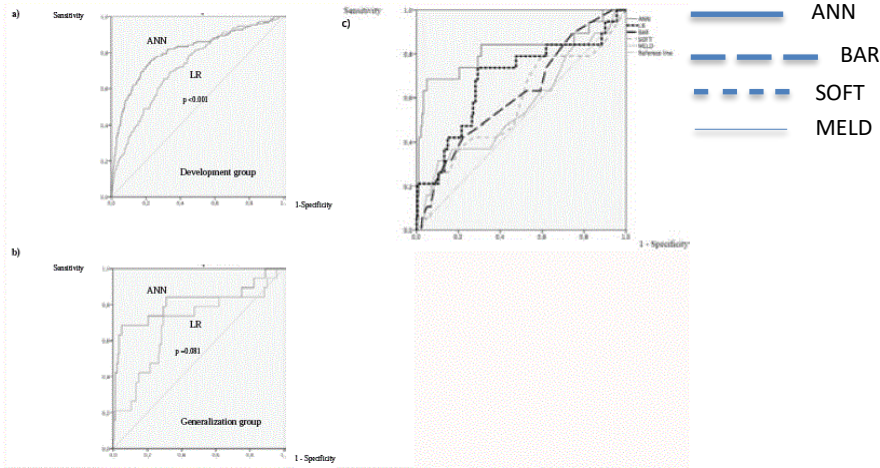


Month	1	3	6
Low Risk	99%	97%	96%
Low-Moderate	97%	94%	92%
High-Moderate	90%	84%	80%
High	72%	62%	56%
Futile	46%	38%	37%

* All groups p<0.01 compared to Low Risk

Rana A, Am J Transplant 2008;8(12):2537-46

Artificial Neural Networks



PREDICTION OF RECEPTOR SURVIVAL BY YEAR OF HEPATIC TRANSPLANTATION

RECIPIENT VARIABLES

Age (years):

BMI (kg/m²):

Cardiovascular risk:

Nephropathy: No Yes

User of diuretics: No Yes

Child:

Etiologic diagnosis:

Hepatocellular carcinoma (HCC):

Bilirubin blood level (mg/dL):

Prothrombin blood level (mg/dL):

Albumin blood level (g/dL):

Creatinine blood level (mg/dL):

Quick index (%):

Portal thrombosis:

Surgery (selective/urgent): Elective Urgent

DONOR VARIABLES

Age (years):

BMI (kg/m²):

Cardiovascular risk:

Cause of death:

Length of stay in ICU (days):

Mean blood pressure:

Use of vasopressors: No Yes

Sodium blood level (mEq/L):

Bilirubin blood level (mg/dL):

ALT blood level (U/L):

Jaundice:

Macroscopic steatosis:

COMPATIBILITY VARIABLES

Blood compatibility:

Gender:

SCORE

Risk NDT CALCULATED for transplant death

Comments

Comments:

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Estaban MB, Clinics in Surgery 2018. 3:2122, Dutkowski P, Ann Surg 2011;254(5):745-53

Conclusions

- We currently have no standard criteria for “too sick to transplant”
- Imperfect understanding leads to selection via the “eyeball” technique
- Outside influences (CMS) run contrary to the notion of transplant benefit and undermine our ability to help many patients who would benefit from transplant
- Critically important to standardize our approach to selection (and de-selection) to create fairness and opportunity
- The criteria to delist or deactivate a patient awaiting liver transplantation requires modeling to better understand the overall interaction of multiple variables leading to transplant survival and guide discussion around if and where a cut-off for “too sick” may be