Historical Perspective of Liver Allocation/Distribution

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No conflicts of interest to report

Organ Allocation Historically

1980's - Voluntary ad hoc basis

1987 - Organ Procurement and Transplantation Network

        1) ICU
        2) Hospitalization
        3) Home

1997 - Minimal Listing CPT ≥ 7
        Severity assessed CPT

2002 - MELD

        Local, Regional, National

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United Network for Organ Sharing (UNOS) Liver Status

▶ <u>Status 2A</u>

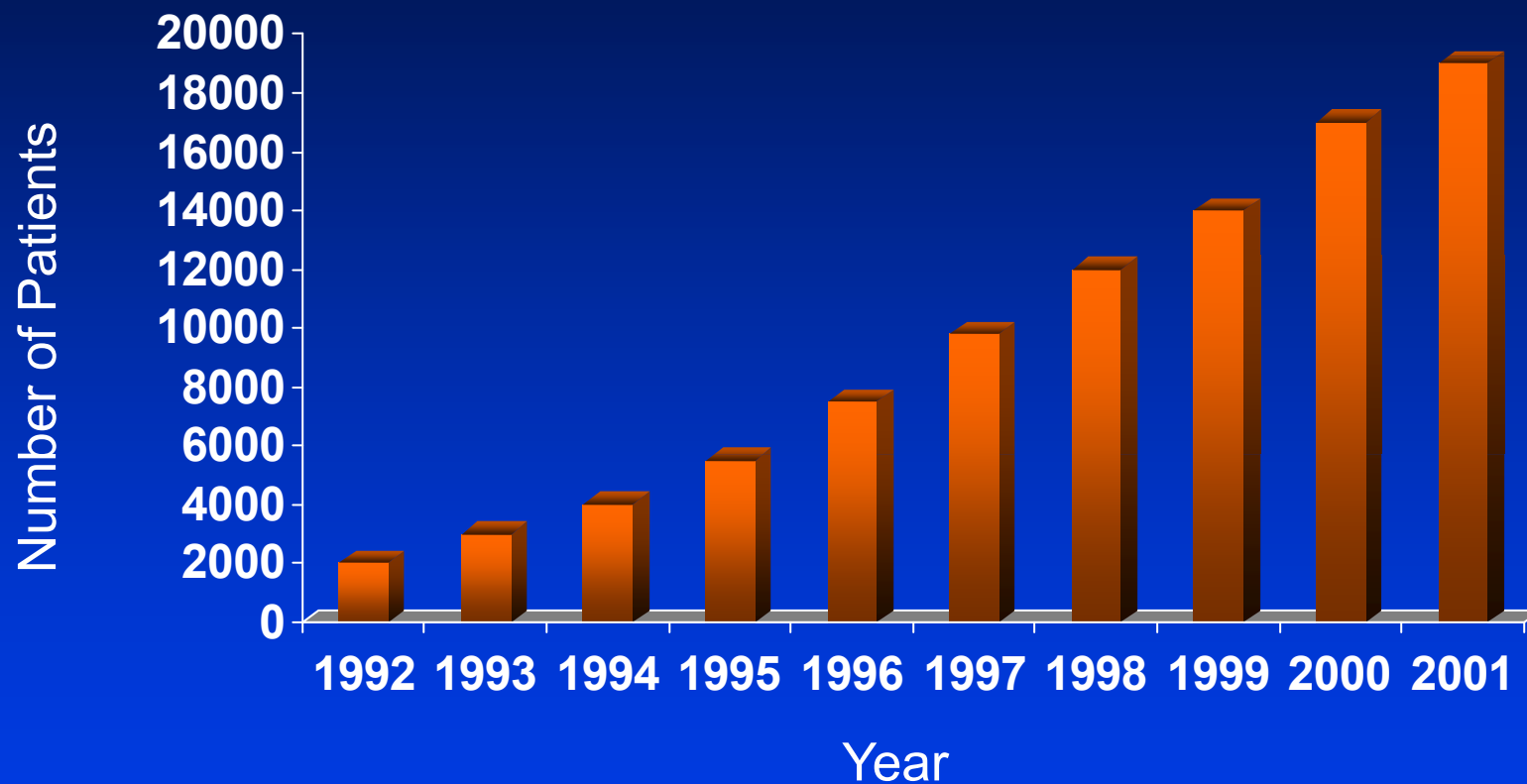   CTP score $\geq$ 10, ICU care, and less than 7 days to live

▶ <u>Status 2B</u>

   CTP score $\geq$ 10 or $\geq$ 7 associated with refractory complications of portal hypertension or hepatocellular cancer meeting the following criteria: 1 lesion < 5 cm, or 3 lesions all < 3cm each, and no evidence of metastatic disease

▶ <u>Status 3</u>

   CTP $\geq$ 7 minimal listing

   ▶ Waiting time

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Registrants on the Liver Waiting List from 1992 to 2001
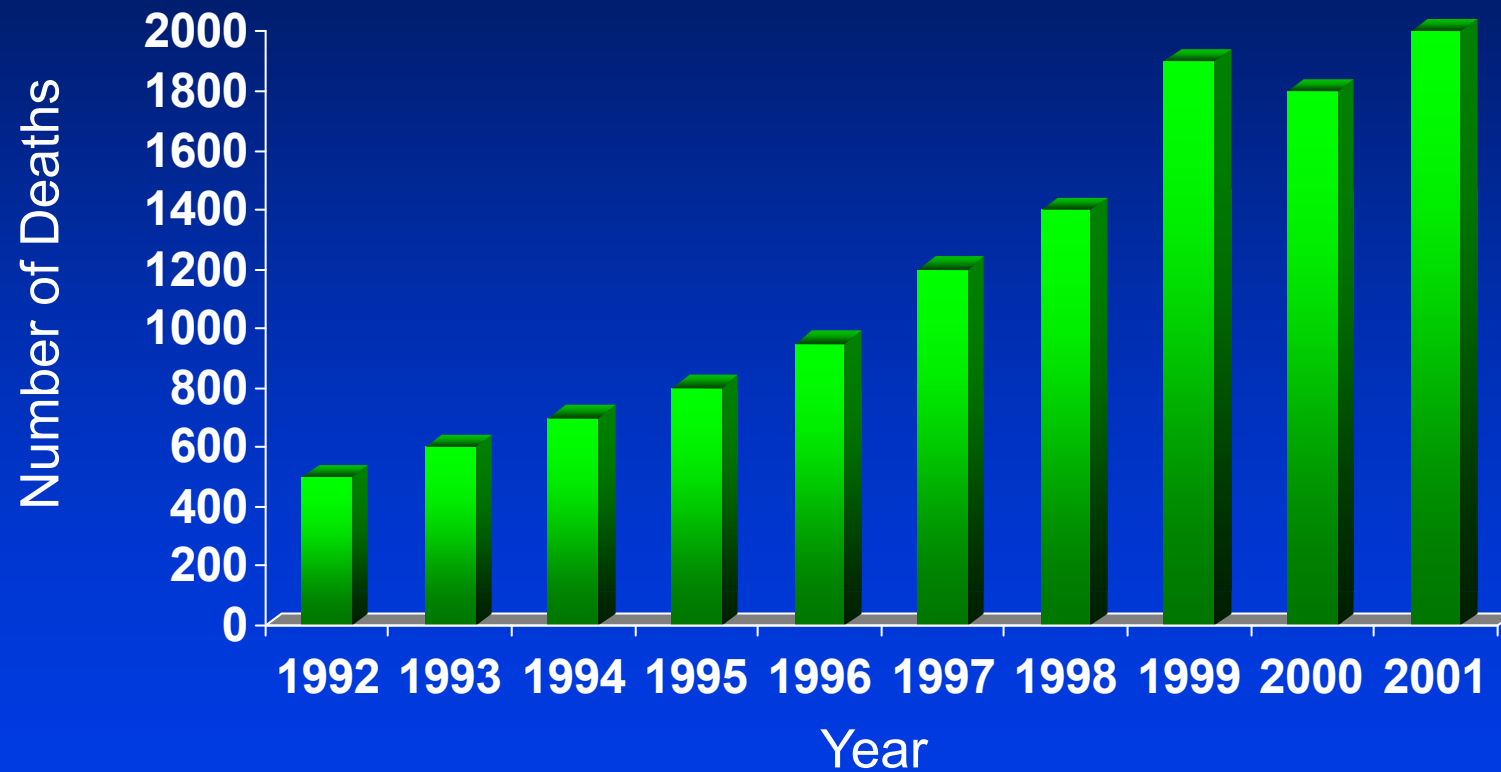
Number of Patients vs. Year

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Registrants Waiting Two Years or More for a Liver Transplant
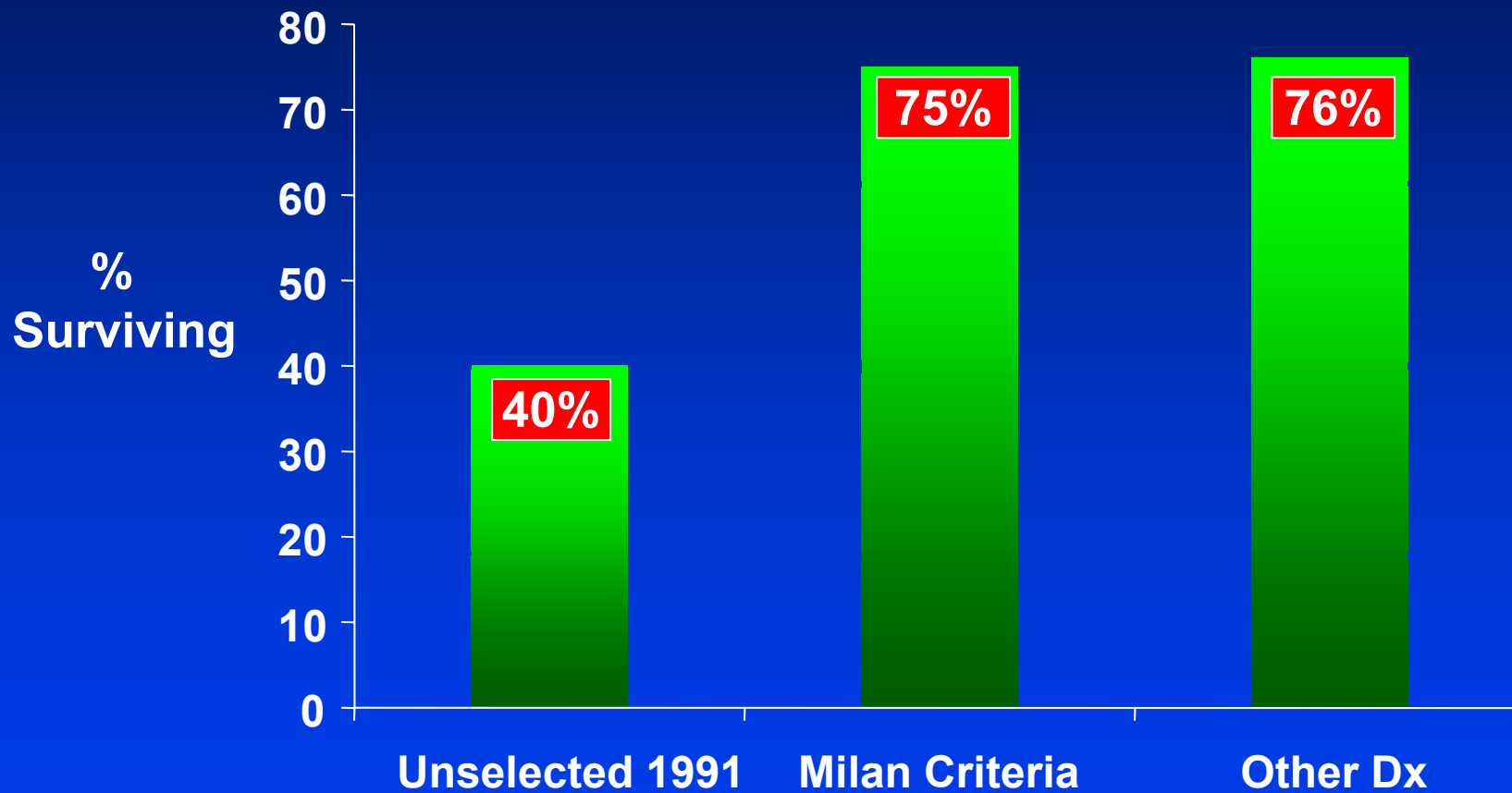
Deaths on the Liver Waiting List from 1992 to 2001
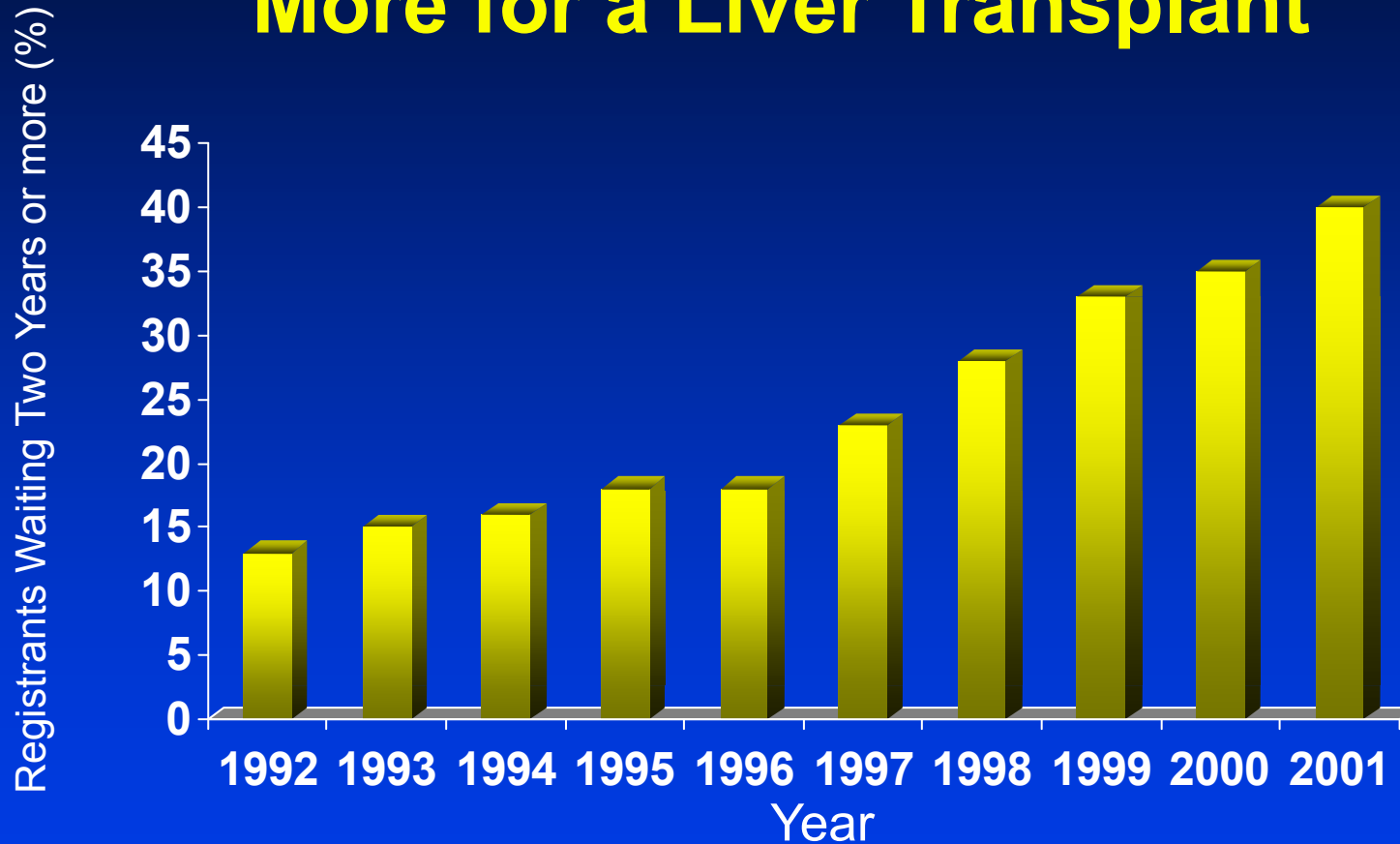
Source: 2002 OPTN/SRTR Annual Report, Table 9.3

Liver Transplantation For HCC
Four -Year Survival
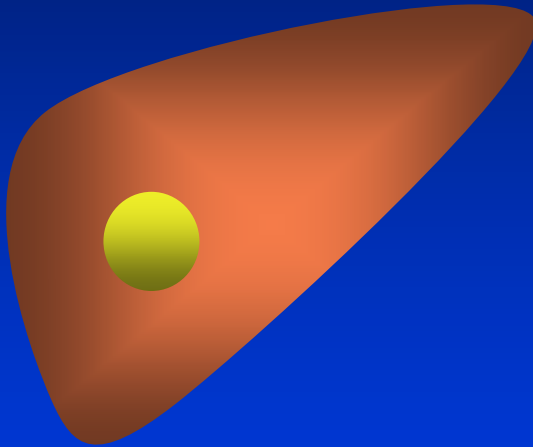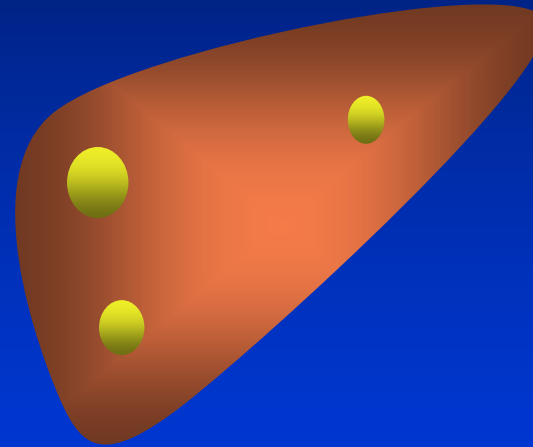
% Surviving

Bar chart showing four-year survival percentages:
- Unselected 1991: 40%
- Milan Criteria: 75%
- Other Dx: 76%

Y-axis: 0, 10, 20, 30, 40, 50, 60, 70, 80

Mazzaferro- N EnglJ Med 1996

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Problems With Old Allocation System for HCC Patients

1) Primarily based on waiting time

2) 45% of patients waited for 2 years

3) 40% of HCC progressed to exceed Milan Criteria-dropouts

4) HCC patients felt to be disadvantaged

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Problems with Allocation Scheme

- Only 3 categories of disease severity
- Waiting list continued to grow - 20,000
- 2B classification extremely broad
- Waiting time became main determinant
- HCC Patients - Long waiting time

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Problems with CTP Score

▶ **Limited number of categories**

▶ **Limited discriminating ability**

▶ **Uses subjective parameters gaming**

▶ **Laboratory variability**

　　　prothrombin time, albumin

▶ **Never validated**

▶ **Creatinine not included**

Pugh's Modification of the Child-Turcotte Classification

Variable	1	2	3
Encephalopathy grade	None	1-2	3 - 4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
Prothrombin time (sec prolonged)	< 4	4 - 6	> 6
Bilirubin (mg/dL)	< 2	2 - 3	> 3
(for cholestatic disease)	(< 4)	(4 - 10)	(> 10)

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Survival in Cirrhosis Based on Level of Renal Dysfunction

P<0.001

Creatinine<1.2 mg/dL

Creatinine1.2-1.5mg/dL

Creatinine>1.5mg/dL

Blackwell: Science, Oxford, UK

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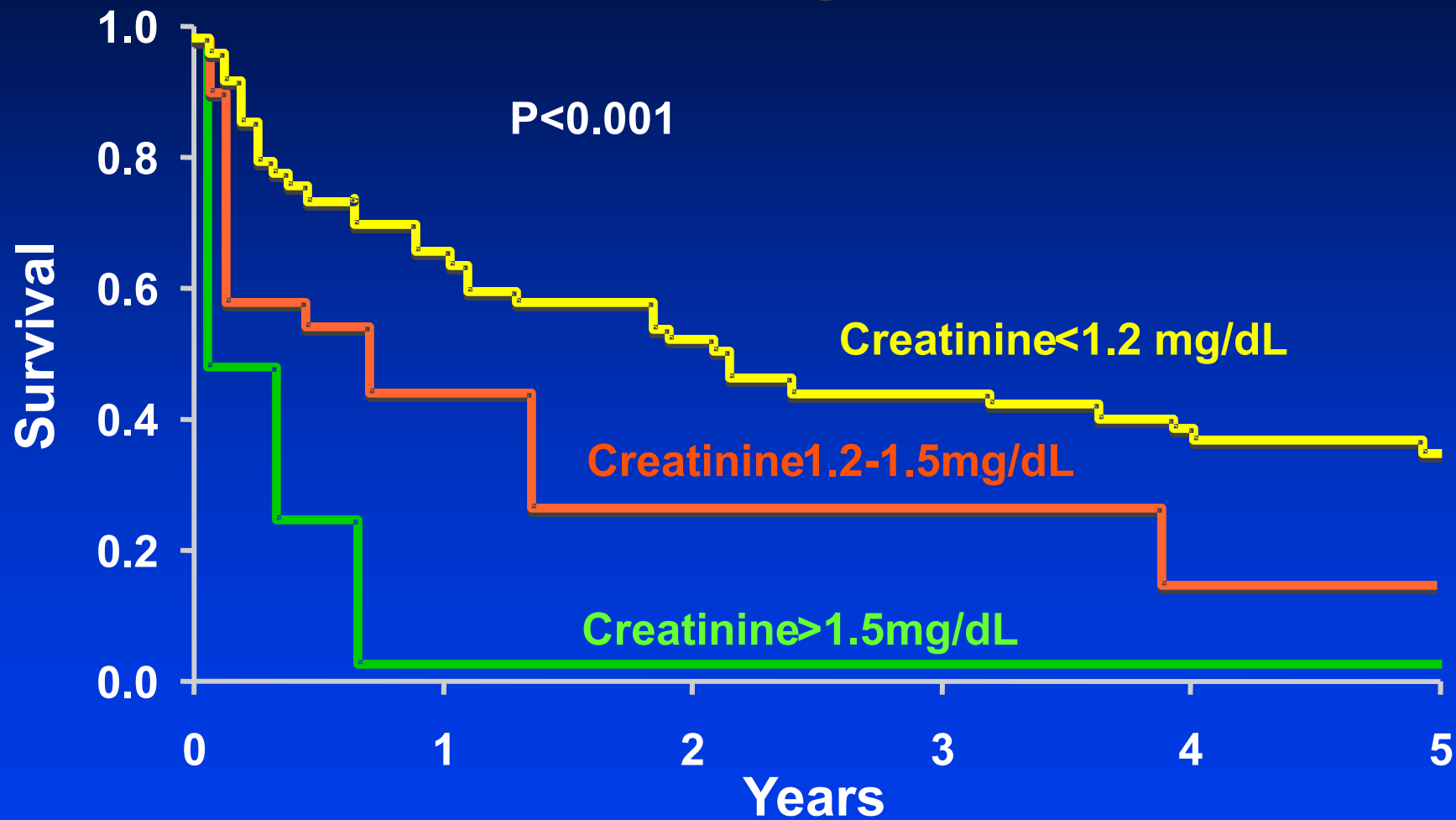
Problems 2000....cont.

▶ **Number of liver waiting list deaths increasing**

▶ **Large centers wanted more organs (National Waiting List)**

▶ **Embellishing CPT score ("everyone is doing it")**

▶ **Makeshift ICU's**

▶ **Disregard for UNOS policy by some**

"I do whatever I have to do to get my patients transplanted"

Rationale for Change

▶ **Waiting time does not reflect medical need**

▶ **Categorical urgency system failed to prioritize large number of waiting patients accurately**

▶ **CTP score**
  - **Subjective**
  - **Never validated for waiting list**
  - **Does not distinguish more ill candidates**

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"Some people change when they see the light, others when they feel the heat."

Caroline Schoeder

Challenge to UNOS

▶ **Develop a liver disease severity index to estimate death in chronic liver disease**

▶ **Needs to be validated clinically and statistically**

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The Mission of UNOS

- As the OPTN contractor, UNOS' mission is:

    to advance organ availability and transplantation

    by uniting and supporting communities

    for the benefit of patients through education, technology
    and policy development

- The Final Rule, effective March 2000, is the framework
    used to guide current and past policy development

Important Concepts from the Final Rule

OPTN/UNOS Allocation Performance Goals

- Allocation should be based upon objective and measurable medical criteria

- Allocation in the order of medical urgency

- Avoid futile transplants

- Promote patient access to transplantation

Important Concepts from the Final Rule

OPTN/UNOS Allocation Performance Goals

- **Minimize** role of waiting times

- Allocation **shall not** be based on the candidate's **place of residence** or place of listing

- Organs shall be distributed over as **broad a geographic area** as feasible

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Ideal Model

- **Small number of variables**
- **Objective parameters**
- **Readily available**
- **Standardized**
- **Applicable to all etiologies**
- **Continuous score reflecting disease severity**
- **Free of political overtones**
- **Easy to use - bedside**

Model for End Stage Liver Disease

Bilirubin

INR

Creatinine

Etiology

Predicted survival in TIPS patients

Survival in TIPS Patients Validation of MELD Score

Legend: Observed survival, Mayo model

Low risk, R <18, n=65
P=0.88

High risk, R ≥18, n=6
P=0.41

Survival (y-axis: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0)
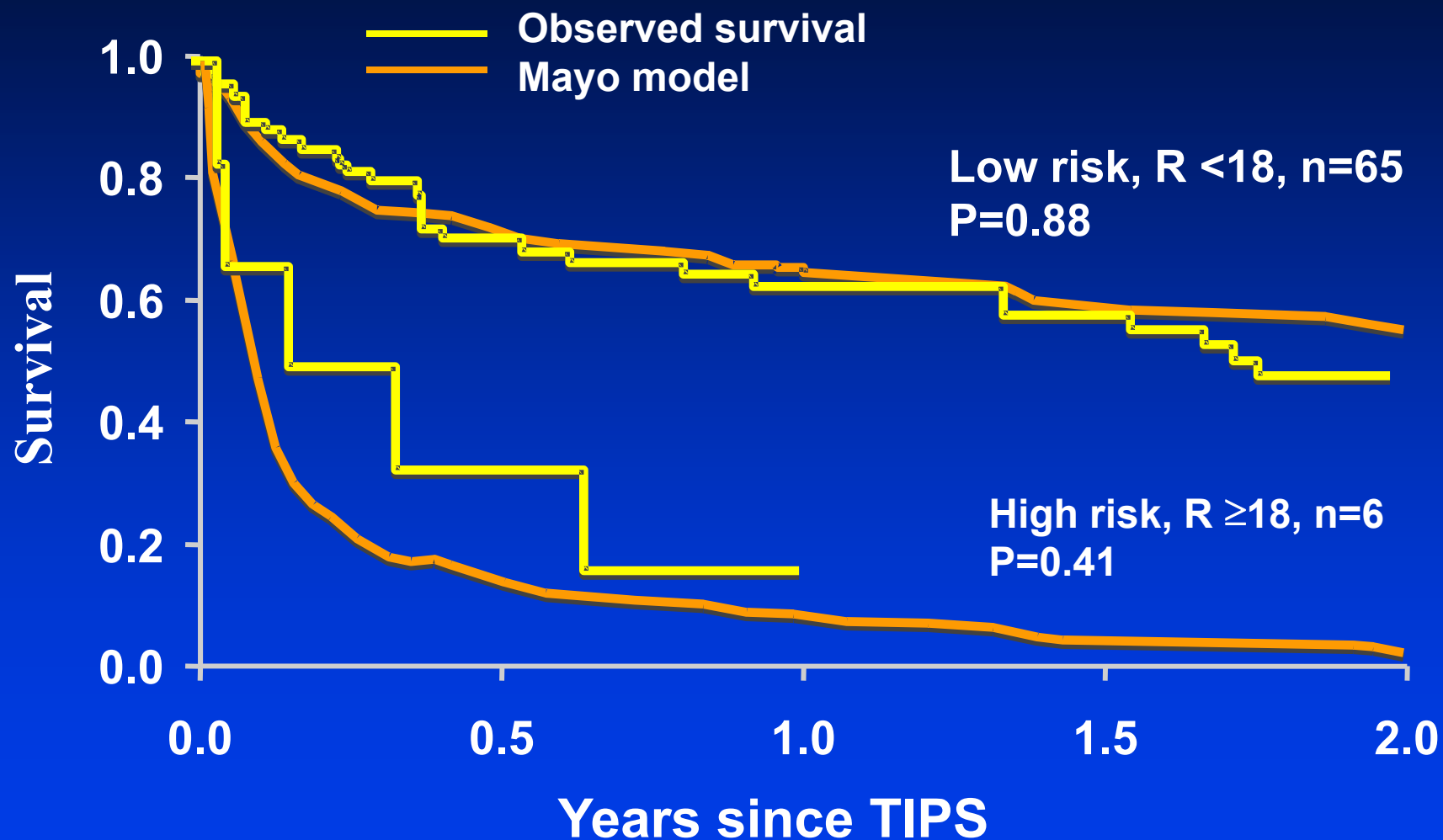
Years since TIPS (x-axis: 0.0, 0.5, 1.0, 1.5, 2.0)

Validation Studies: Child-Pugh vs MELD
3-Month Survival

Patients	No.	MELD Concordance (95% CI)		Child-Pugh Concordance (95% CI)
Hospitalized	282	0.88	0.83-0.93	0.84 (0.78-0.9)
Historical	1,179	0.77	0.74-0.81	
Outpatient	491	0.81	0.72-0.90	0.73 (0.64-0.8)
PBC	303	0.87	0.70-1.00	
UNOS (waiting list)	311	0.83	0.76-0.87	0.73 (0.66-0.79)

Concordance >0.7 indicates clinically useful test; >0.8 excellent test; >0.9 validation of laboratory tests

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How will Complications Such as SBP, Variceal Bleed, Encephalopathy, and Hydrothorax be Handled?

The data supports that whether you live or die depends on the severity of your liver disease
and not on whether you develop a complication

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Effect of Adding Risk Factor to MELD Score in Predicting 3-Month Mortality

	Concordance	
Risk factor	MELD alone	MELD + risk factor
SBP	0.77	0.77
Variceal bleed	0.87	0.88
Ascites	0.87	0.88
Encephalopathy	0.87	0.88

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Significant Variables that Could Not be Used in Model

- Etiology

- Recipient age

- Race

- Gender

- Transplant Center

Final Model – Creatinine, INR, Bilirubin

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Deceased Donor Liver Allocation

February 2002 Changes:

Child-Turcotte-Pugh Score $\longrightarrow$ $\longrightarrow$ MELD Score

- Ascites   - Creatinine

- Encephalopathy   - Bilirubin

- Bilirubin   - Protime INR

- Protime INR

- Albumin

$$\text{ore} = 0.957 \times Log_e \text{ (creatinine mg/dL)} + 0.378 \times Log_e \text{ (bilirubin mg/dL)} +$$
$$\text{og}_e \text{ (INR)} + 0.643$$

UNOS Study

- **11/99 to 12/01**

  Data on 3,437 patients

  MELD Score

  3 month outcomes

  a) transplanted
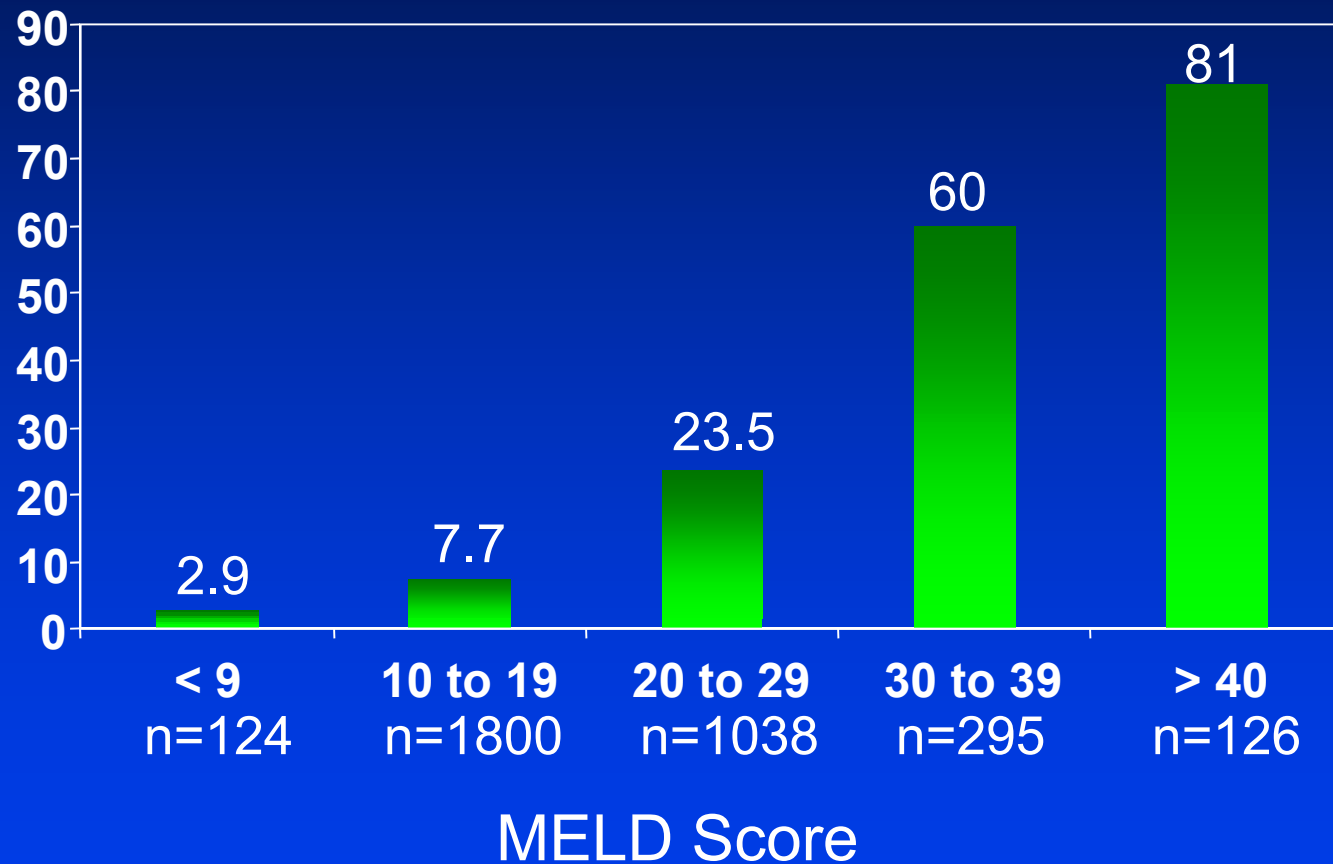
  b) died

  c) removed - too sick

  d) alive

  Allocation was by old scheme

  HCC/metabolic cases not analyzed

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3-Month Mortality Based on Listing MELD Score

MELD Score	Value
< 9 n=124	2.9
10 to 19 n=1800	7.7
20 to 29 n=1038	23.5
30 to 39 n=295	60
> 40 n=126	81

MELD Score

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3-Month Mortality Based on Listing CTP Score

% Death (y-axis): 0, 10, 20, 30, 40, 50

- 7 - 9: 5.6
- 10 - 12: 13.4
- 13 - 15: 48.5

CTP (x-axis)

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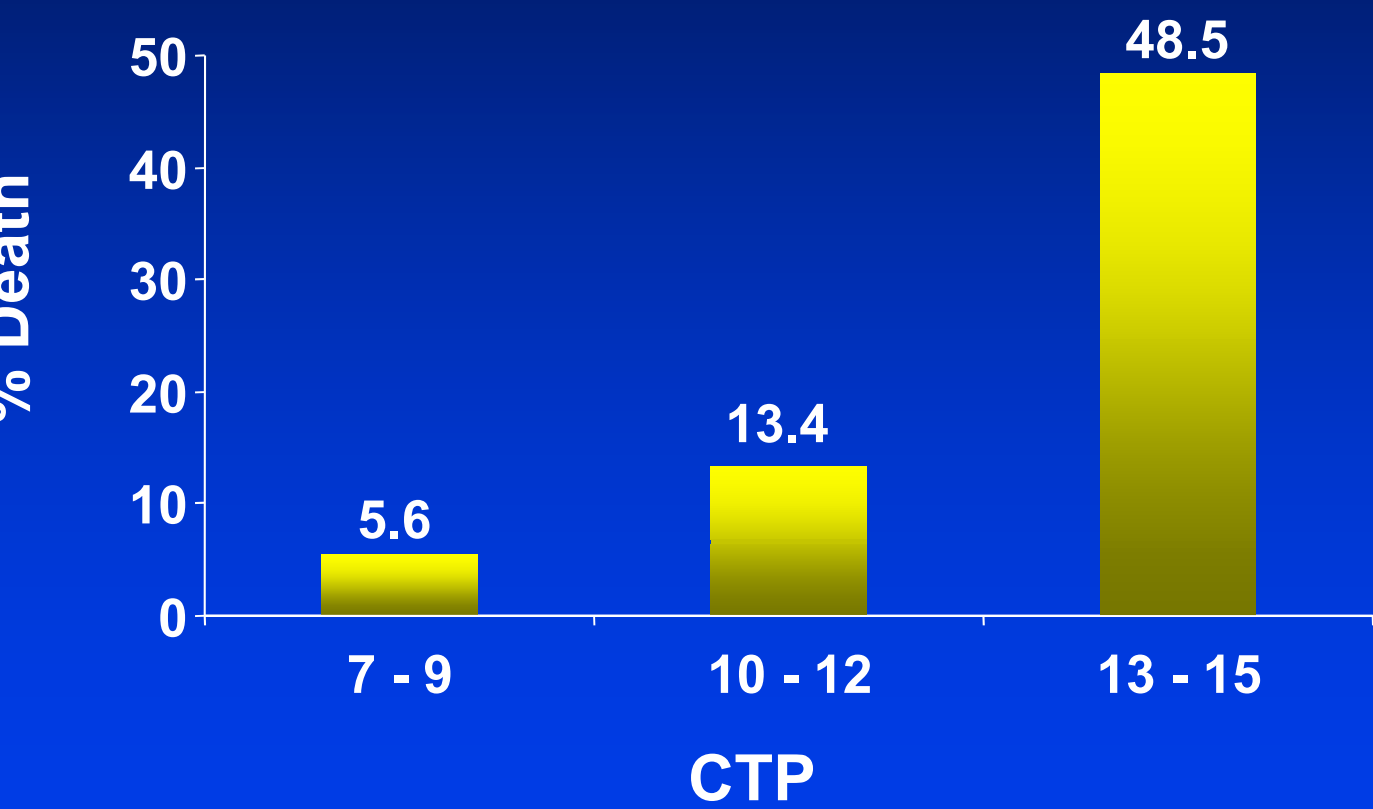
OC Curve for 3-Month Mortality on UNOS Waiting List

MELD

CTP

p < 0.001

MELD Area = 0.83
CTP Area = 0.76

1

.8

.6

.4

.2

0

0   0.2   0.4   0.6   0.8   1

1-Specificity

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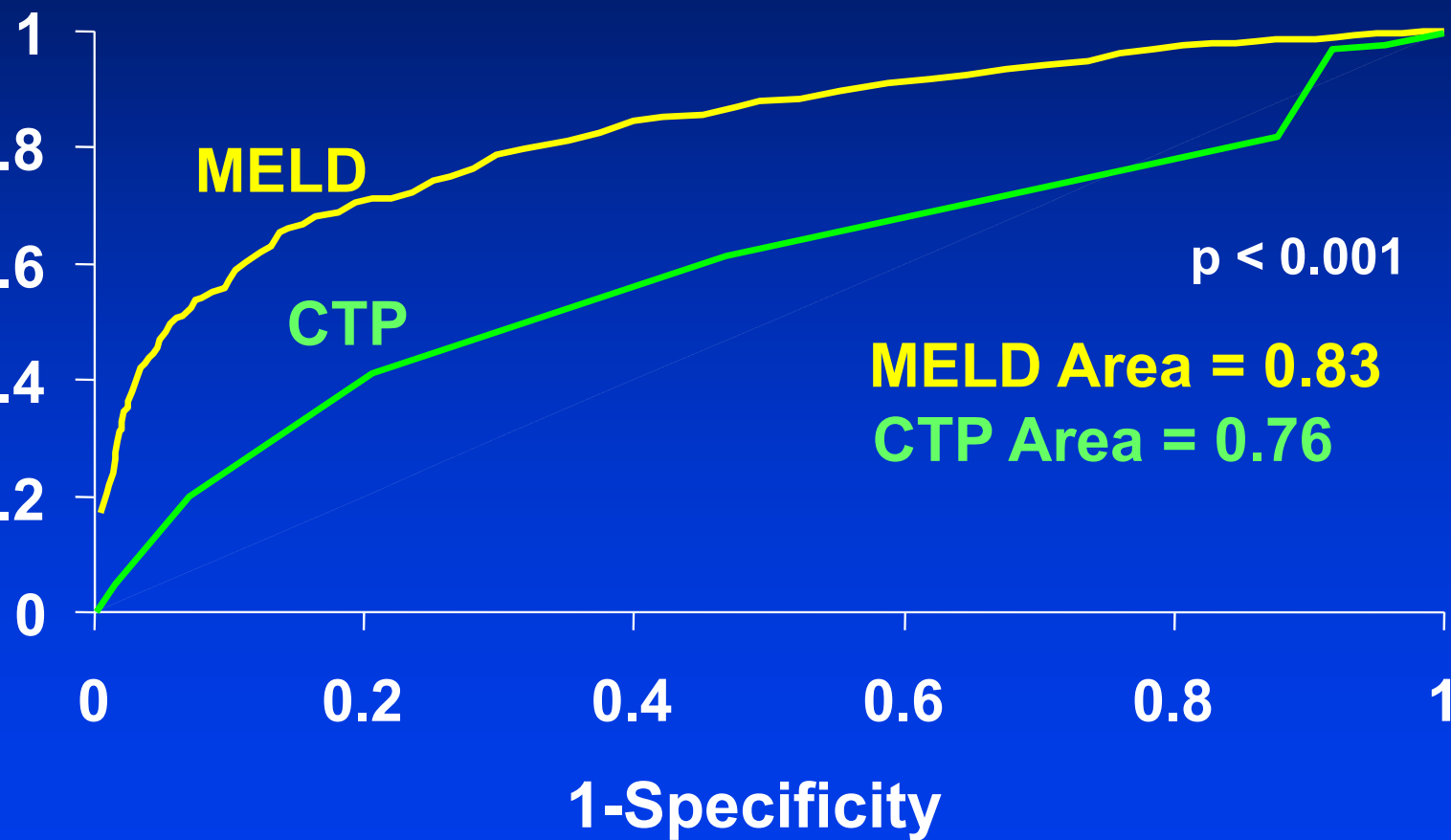
Current Liver Allocation System is Based Upon Medical Urgency: MELD Score

Relative Risk of Waitlist Death

log(RR)

Status1: Fulminant

Status1: PNF/HAT

Other

HCC

**Patients Added to the List
2/27/02-2/26/03**

Lab MELD

*Censored at earliest of transplant, removal from the waitlist for reason of improved
condition, next transplant, day 60 at status 1 or end of study; unadjusted; includes exception

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Pediatric Liver Disease Severity Scale SPLIT Database

- 884 children with chronic liver disease

- 779 not in ICU at listing

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Pediatric Univariate Analysis of Risk Factors

<div align="center">

Outcome (P)

Parameter	Death/ICU	Death
Age <1 yr	<0.001	<0.0001
Albumin	<0.001	<0.0062
Total bilirubin	<0.001	<0.0001
INR	<0.001	<0.0001
Growth failure	<0.0009	NS
Creatinine	NS	NS

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Comparison of Severity Scores Using ROC

	Outcome	
	Death/ICU	**Death**
PELD	0.821	0.916
MELD	0.705	0.824

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MELD and PELD Mortality Risks at Three Months

Survival (%) vs Severity Score

- PELD: SPLIT Patients (red)
- MELD: National Waitlist (yellow)

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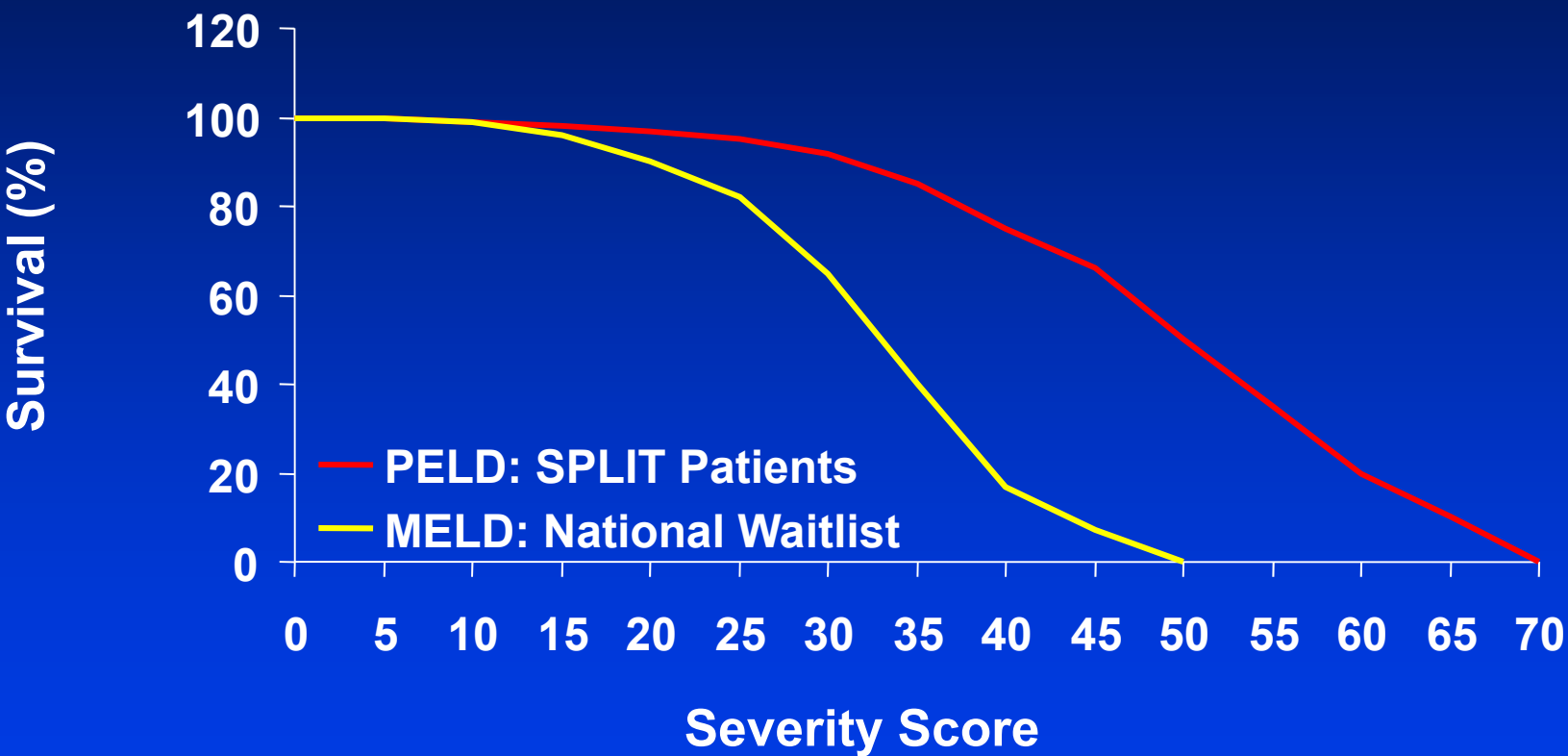
MELD / PELD Advantages

Continuous measure of liver disease severity

Based on objective parameters

Accurate predictor of 3 months mortality

Independent of complications of portal hypertension

Independent of etiology

Better than C.T.P.

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Hepatocellular Cancer Patients Challenge

• Most had MELD scores < 10

• Equate probability of becoming non transplantable to risk of dying with chronic liver disease while on waiting list

Hepatocellular Carcinoma

	3-month mortality	MELD Score
Single lesion ⊕ 2 cm	15	24
Single lesion 2 ⊕ 5 cm or 2-3 lesions all ⊕ 3 cm	30	29

d 10% mortality every 3 months until transplanted,
ad, or not transplantable - must apply for this.

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ELD/PELD Allocation Scheme Initiated on February 27, 2002

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TITANIC

.titanicmovie.com

Letter to the HHS Secretary from AASLD

December 16, 2002

*ELD Committee should be held
ponsible for an increasing number of
aths on the waiting list since the start
the new allocation system in February
02"*

Adrian DiBisceglie
Bruce Bacon
Jules Dienstag
Jeff Crippin

MELD / PELD Impact Summary

►**Excellent predictor of pretransplant survival**

►**Decreased registrations (MELD < 10)**

►**Decreased death rate on waiting list**

►**Transplant sicker patients**

►**Increase transplant of HCC patients**

►**Post transplant survival unchanged**

►**Resource utilization correlates with MELD**

►**Better defining survival benefit - optimal timing**

►**Evidence-based decision-making**

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2 Main Aspects of the Organ Transplant Equation

Allocation: the way candidates are ranked within a distribution unit (i.e., by medical urgency statuses or scores)

Distribution: a specific group of waiting list candidates (currently defined as local i.e. DSA, regional, or national)

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Current Distribution Unit
58 OPO/Donor Service Areas

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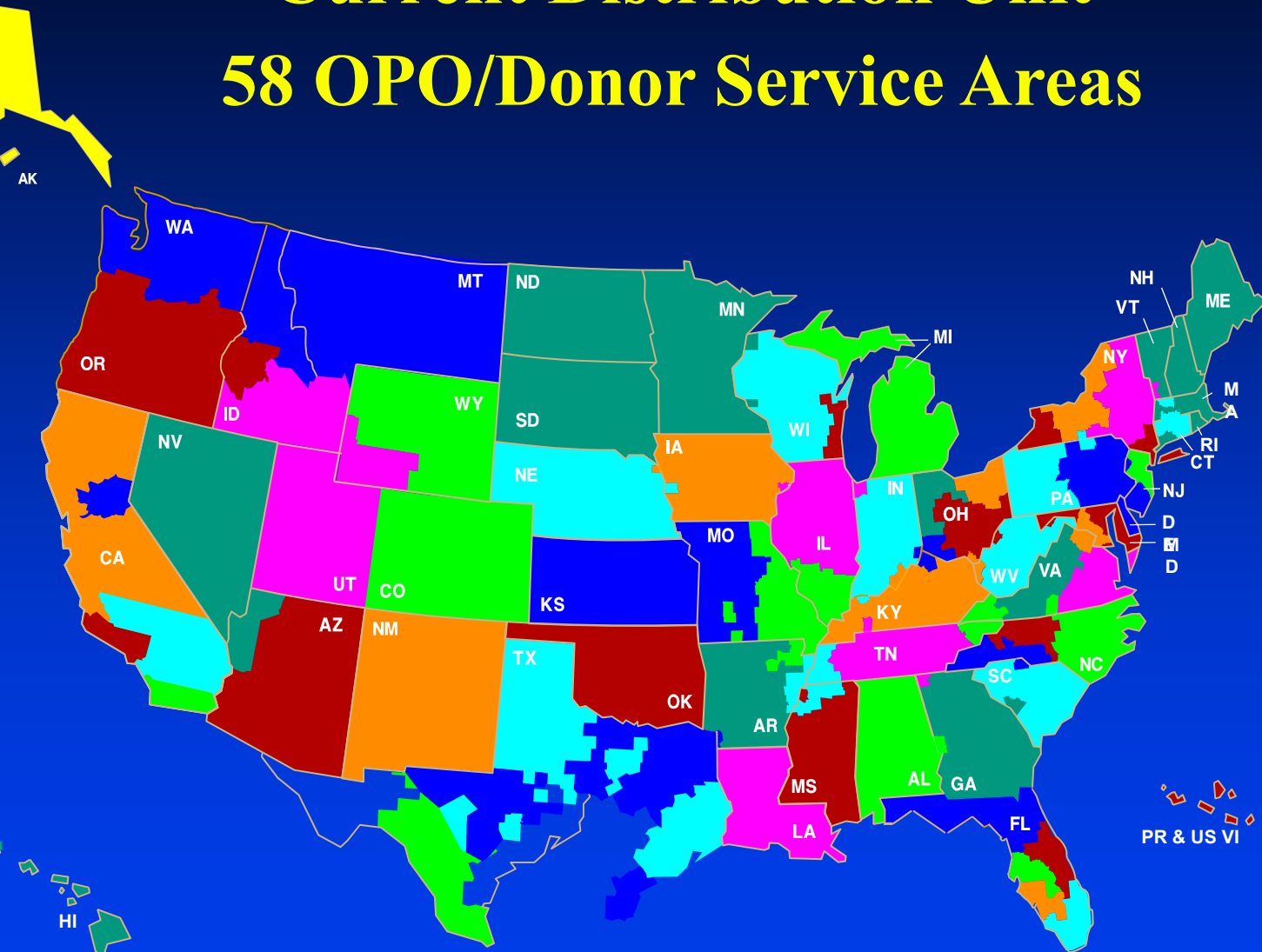
Donor Service Areas

- **Arbitrarily defined as area of OPO**
- **Wide variability in size and population**
  1.3 - 18.7 million population base
- **Performance measures not enforced**
  Consent rate: 37%-88%
  Conversion rate: 45%-93%

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s **Angeles Times**   **June 11, 2006**

lth : Transplant inequality / A Times Special Report

th by Geography

ents' chances of getting new organs in time to save their lives vary
y based on where they live. The situation is most dire for people
ing livers.

lan Zarembo, Times Staff Writer

*the world of organ transplantation, location is
rything."*

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Impact of a single center OPO
Percent of Recipients with MELD < 20
Transplanted within 30 days of Listing

U / Wisconsin	32.5%
Mayo Clinic	1.7%
U / Minnesota	9.0%
Northwestern	8.6%