Sensitivity of Liver Function Classification Systems for Exposure Changes

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- The author has no disclosures related to the content of this presentation

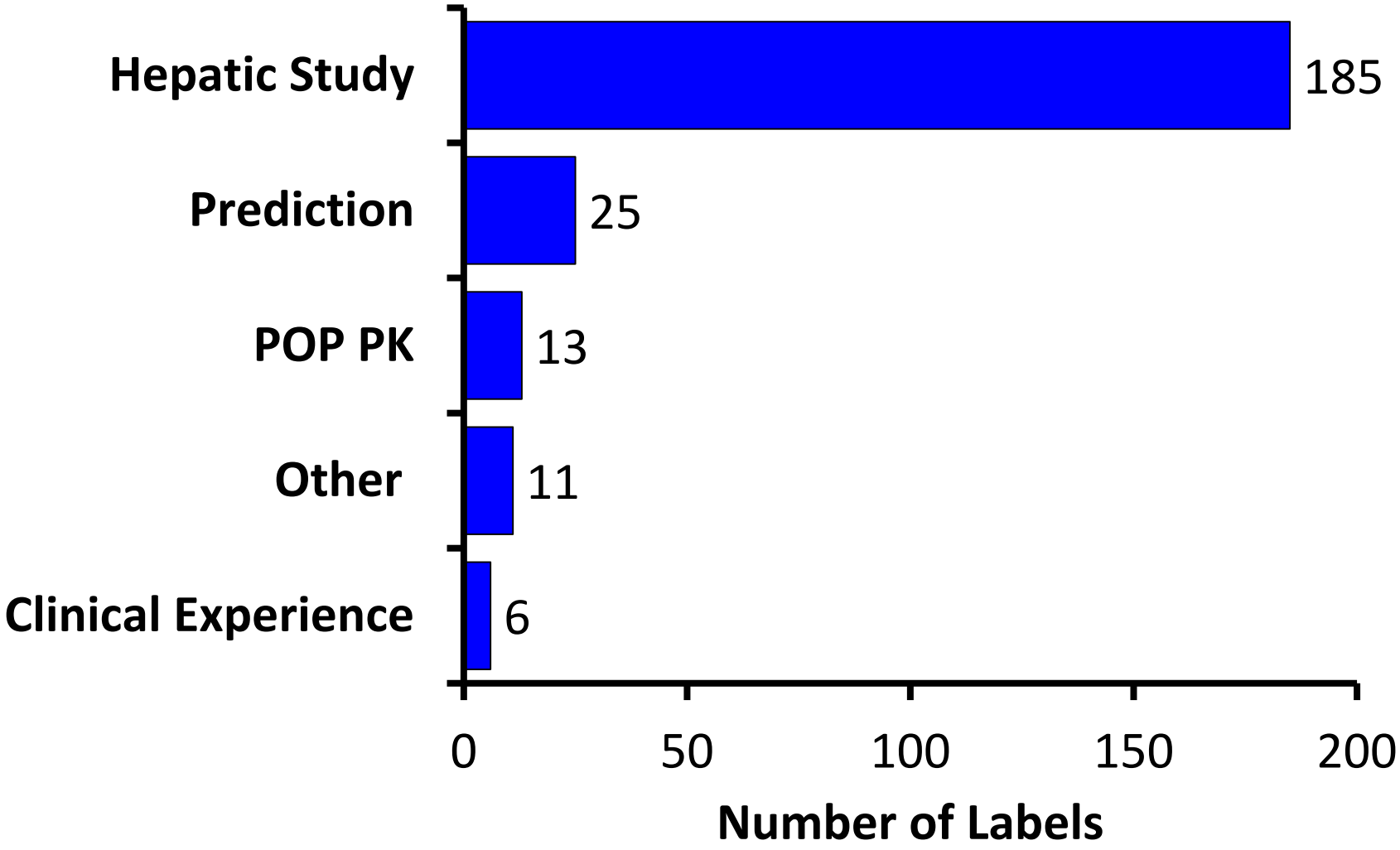
Outline

- Landscape of Hepatic Impairment Studies
- Sensitivity of Liver Function Classification Systems for Exposure Changes

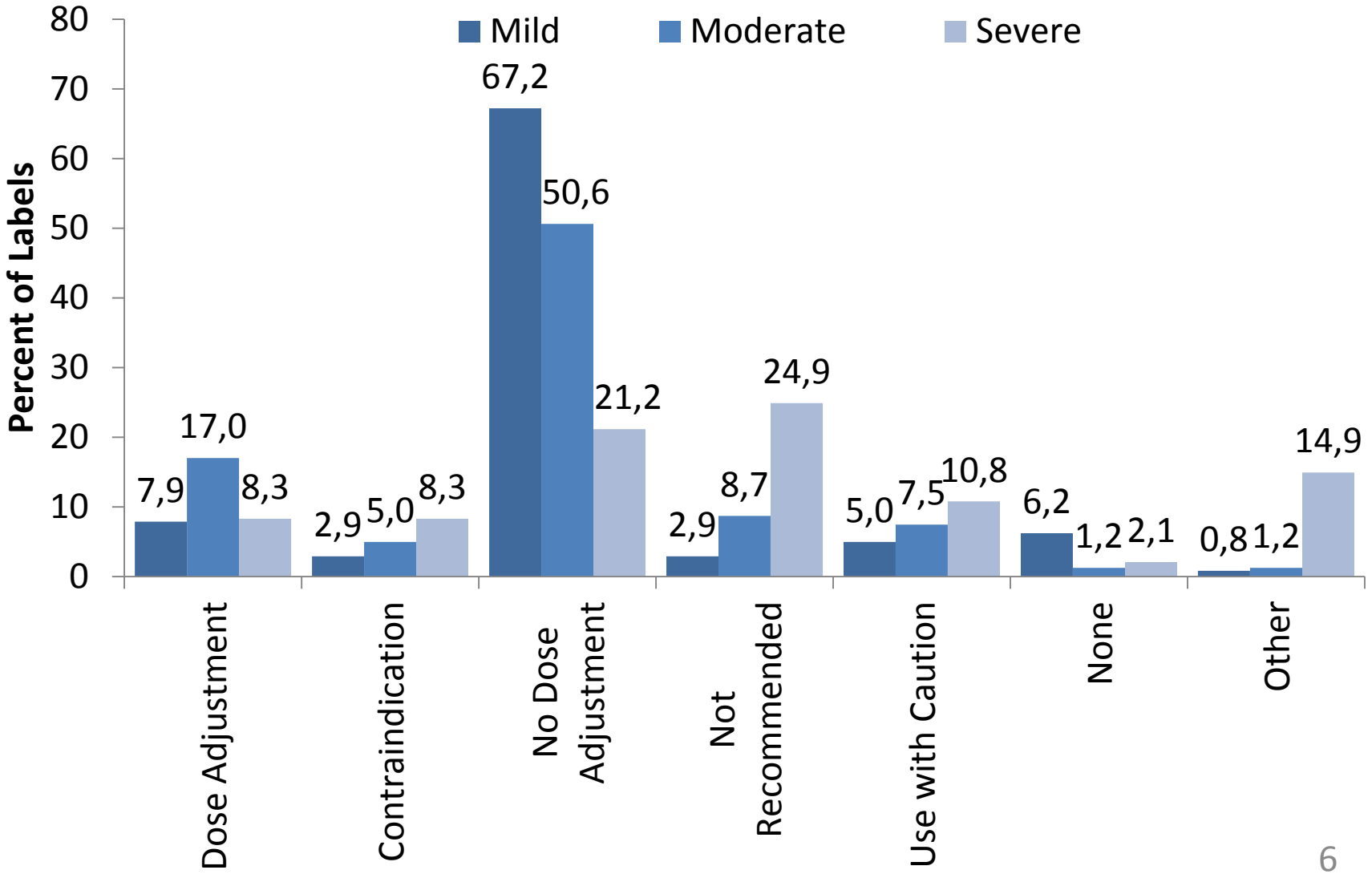
NME Labels Survey

- A total of 341 NME labels (2000-2014) were surveyed
- 240 (~70%) labels with labeling language regarding respective drug(s) administration in patients with hepatic impairment

NME Labels Information Source



Distribution of Label Recommendations

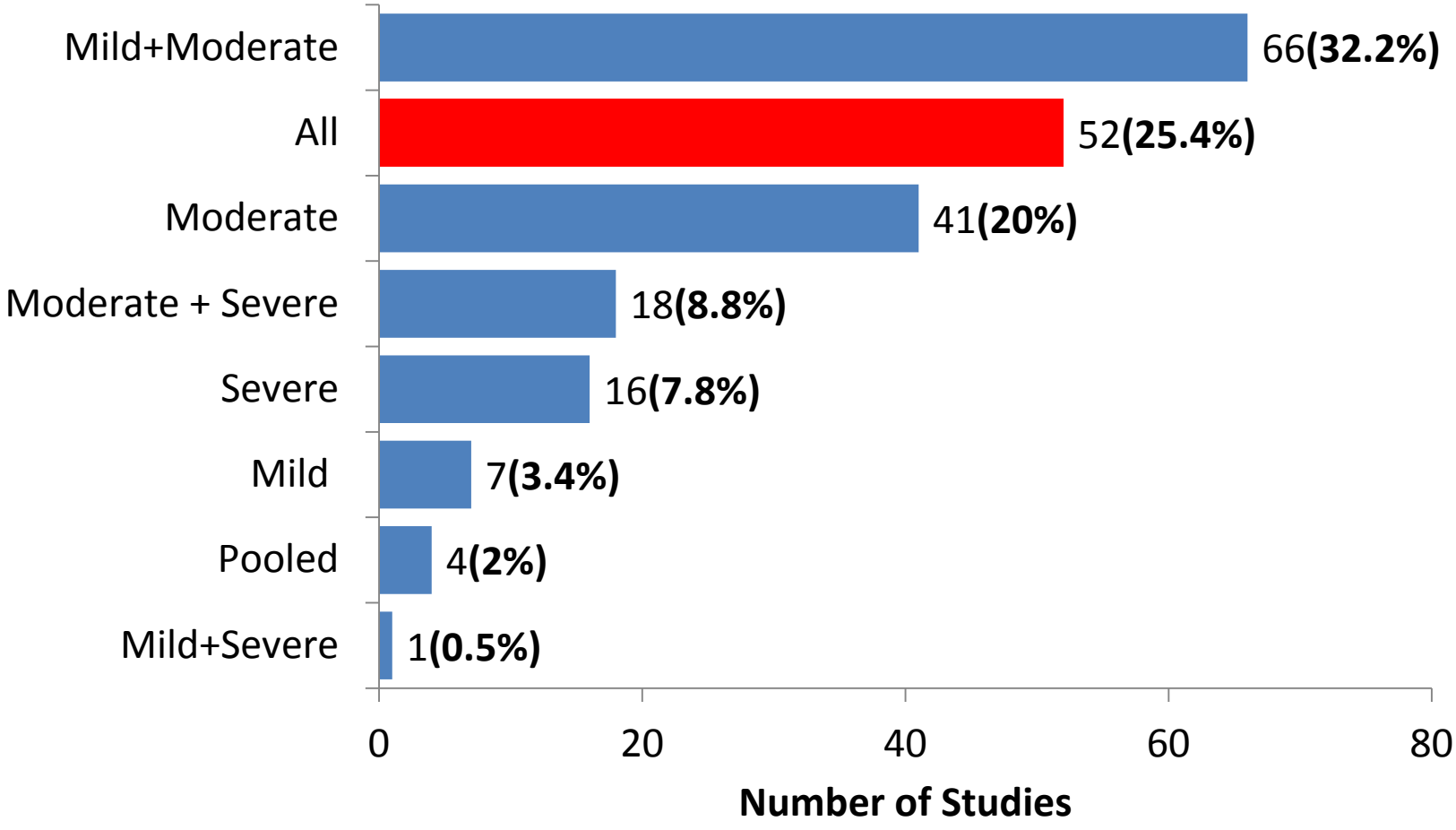


Hepatic Impairment Studies

- A total of 205 studies were identified in 185 NMEs labels (54%).
- Hepatic Impairment Classification

Liver Impairment Classification System	Number (Percentage)
Child-Pugh Classification	195 (95%)
NCI Criteria	4 (2%)
Not Available	5(2.4)
Child-Pugh Classification +NCI Criteria	1 (0.5%)

Distribution of Hepatic Impairment Arms



Sensitivity of Liver Function Classification Systems for Exposure Changes

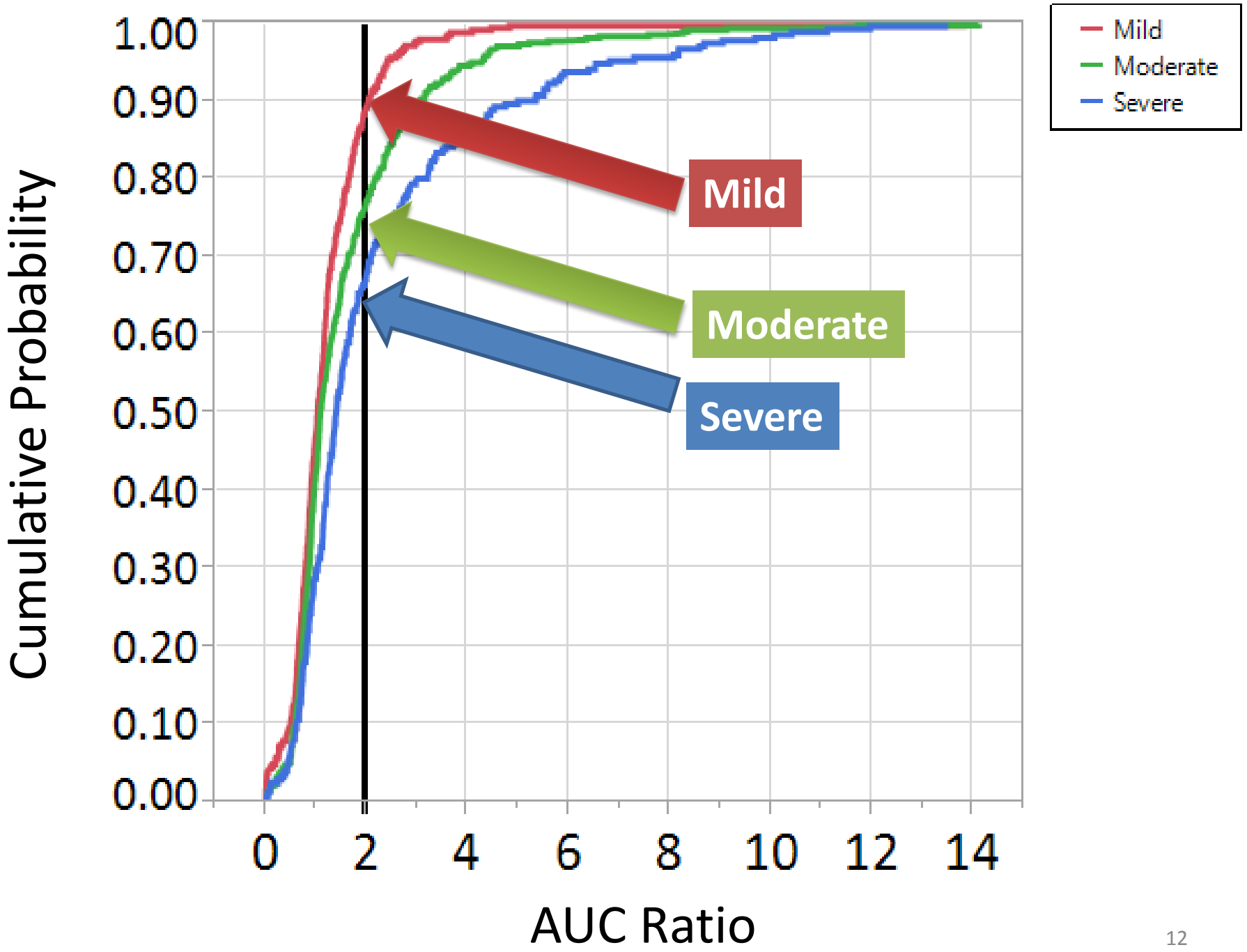
Database

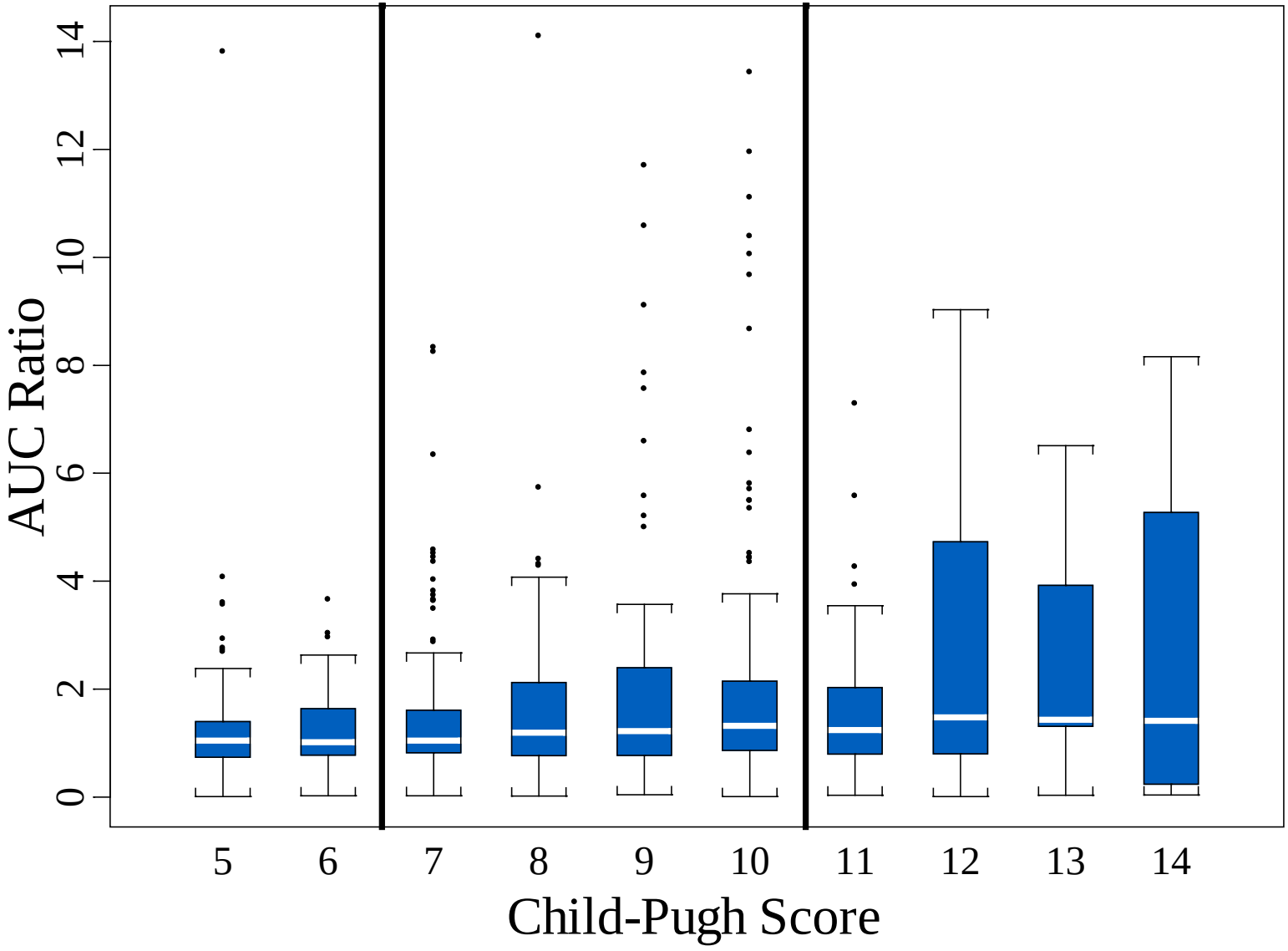
- 65 Studies
- Total Number of Subjects is 1841
  - Normal = 692
  - Mild=351
  - Moderate=512
  - Severe=286

Child-Pugh Classification

Item	1 Point	2 Points	3 Points
Encephalopathy grade	None	Stage 1 or 2	Stage 3 or 4
Ascites	Absent	Slight	Moderate to Severe
Serum bilirubin, mg/dL	< 2	2-3	>3
Serum albumin, g/dL	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

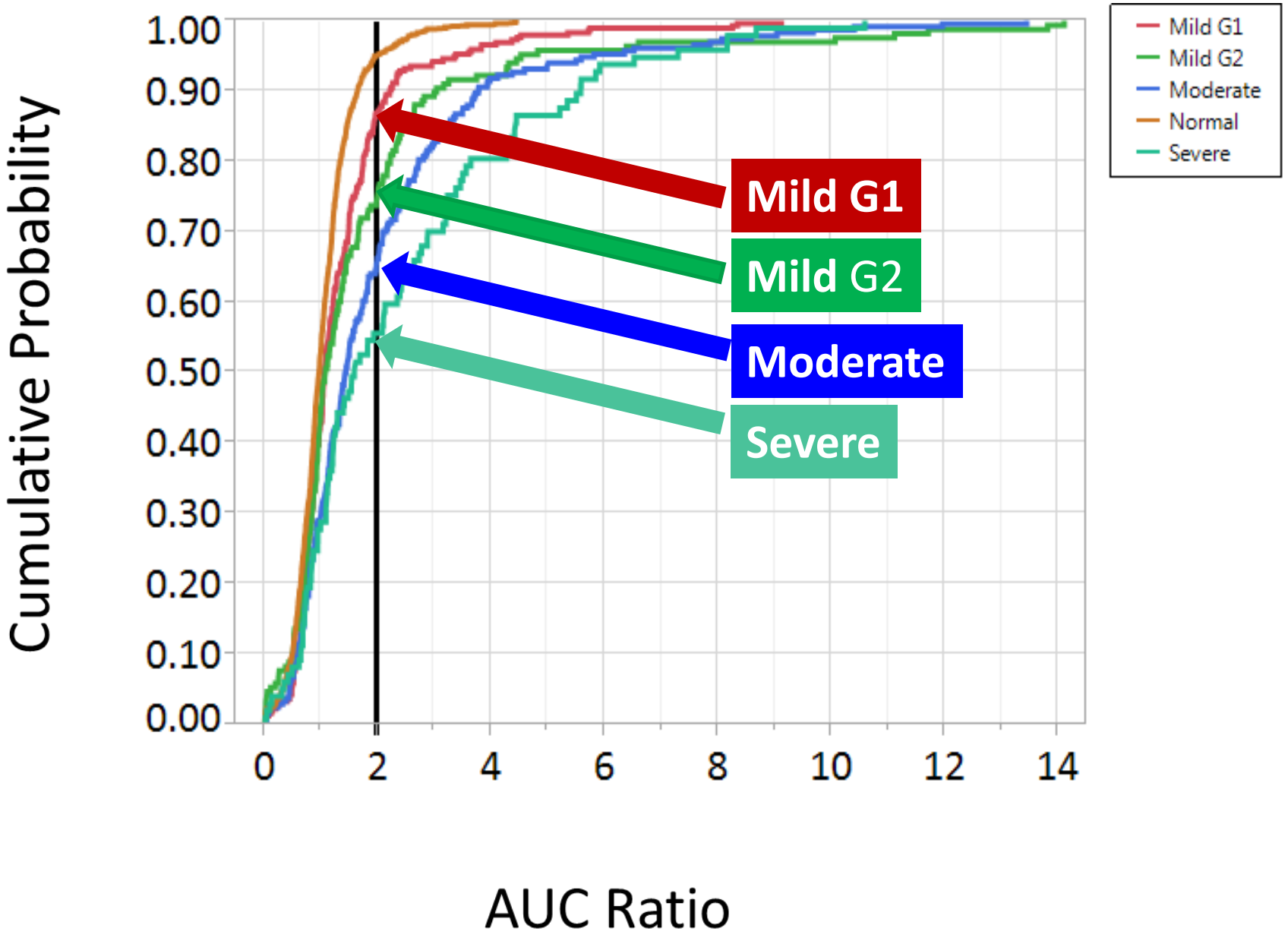
Hepatic Impairment Group	Child-Pugh Score
Mild	5-6
Moderate	6-9
Severe	10-15


Cumulative Probability
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
2
4
6
8
10
12
14
AUC Ratio
Mild
Moderate
Severe
Mild
Moderate
Severe


AUC Ratio
0
2
4
6
8
10
12
14
5
6
7
8
9
10
11
12
13
14
Child-Pugh Score

NCI Criteria

Liver Test	Normal	Mild GB1	Mild GB2	Moderate	Severe
Total Bilirubin	≤ ULN	≤ ULN	>1.0x – 1.5x ULN	>1.5x – 3xULN	>3x ULN
AST	≤ ULN	> ULN	Any	Any	Any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0.40
0.30
0.20
0.10
0.00
0
2
4
6
8
10
12
14
AUC Ratio
Mild G1
Mild G2
Moderate
Normal
Severe
Mild G1
Mild G2
Moderate
Severe

Child-Pugh vs. NCI Criteria

		Child-Pugh Classification			
		Normal (N=658)	Mild (N=334)	Moderate (N=473)	Severe (263)
NCI Criteria	Normal	94.7%	53.6%	22.4%	3.4%
	Mild G1	2.6%	31.4%	32.3%	10.6%
	Mild G2	2.3%	12.0%	16.5%	13.7%
	Moderate	0.5%	3.0%	23.0%	45.2%
	Severe	0.0%	0.0%	5.7%	27.0%

Model for End Stage Liver Disease

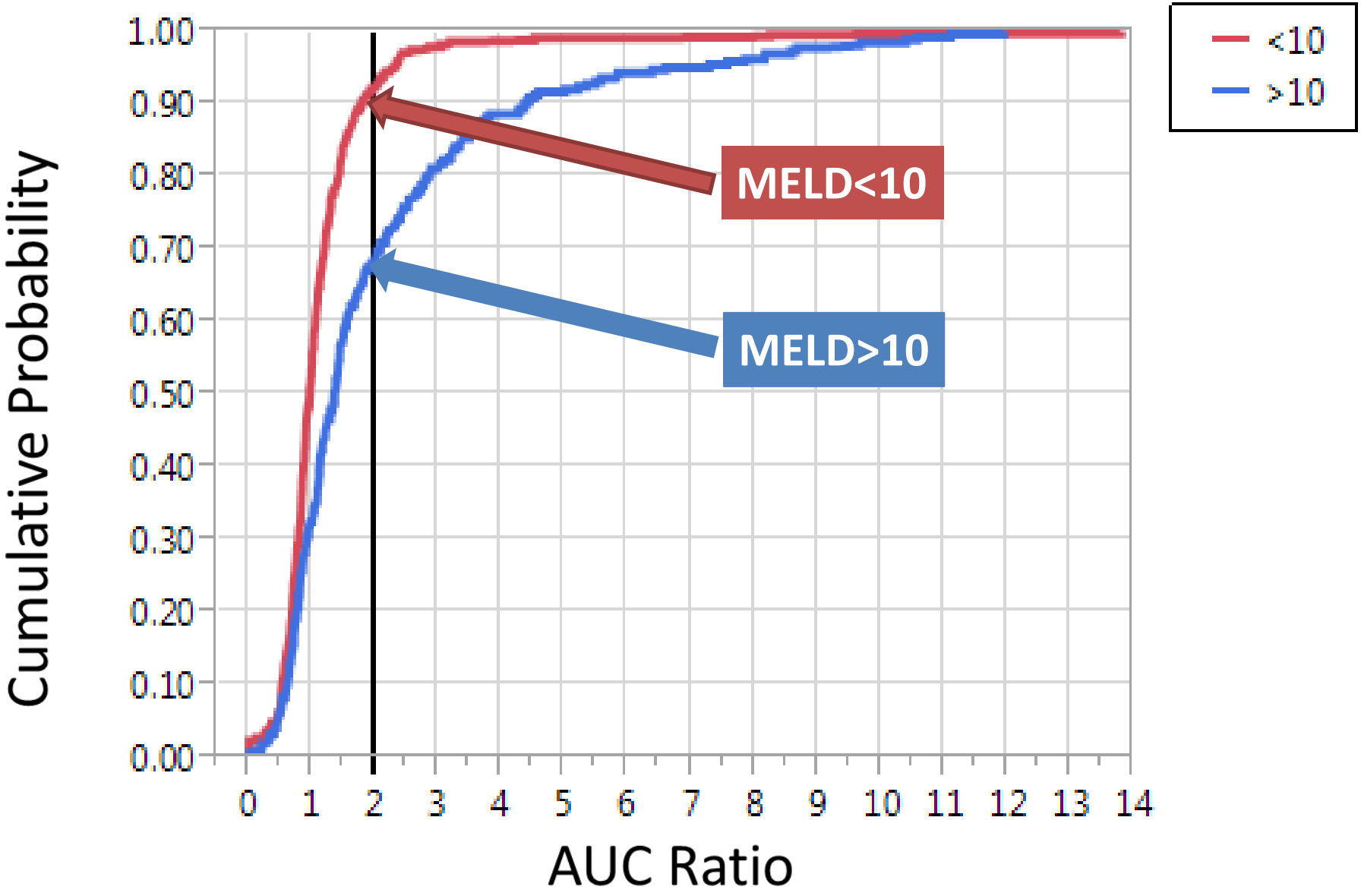
MELD score =

3.78 (ln Serum Bilirubin) +

11.2 (ln INR) +

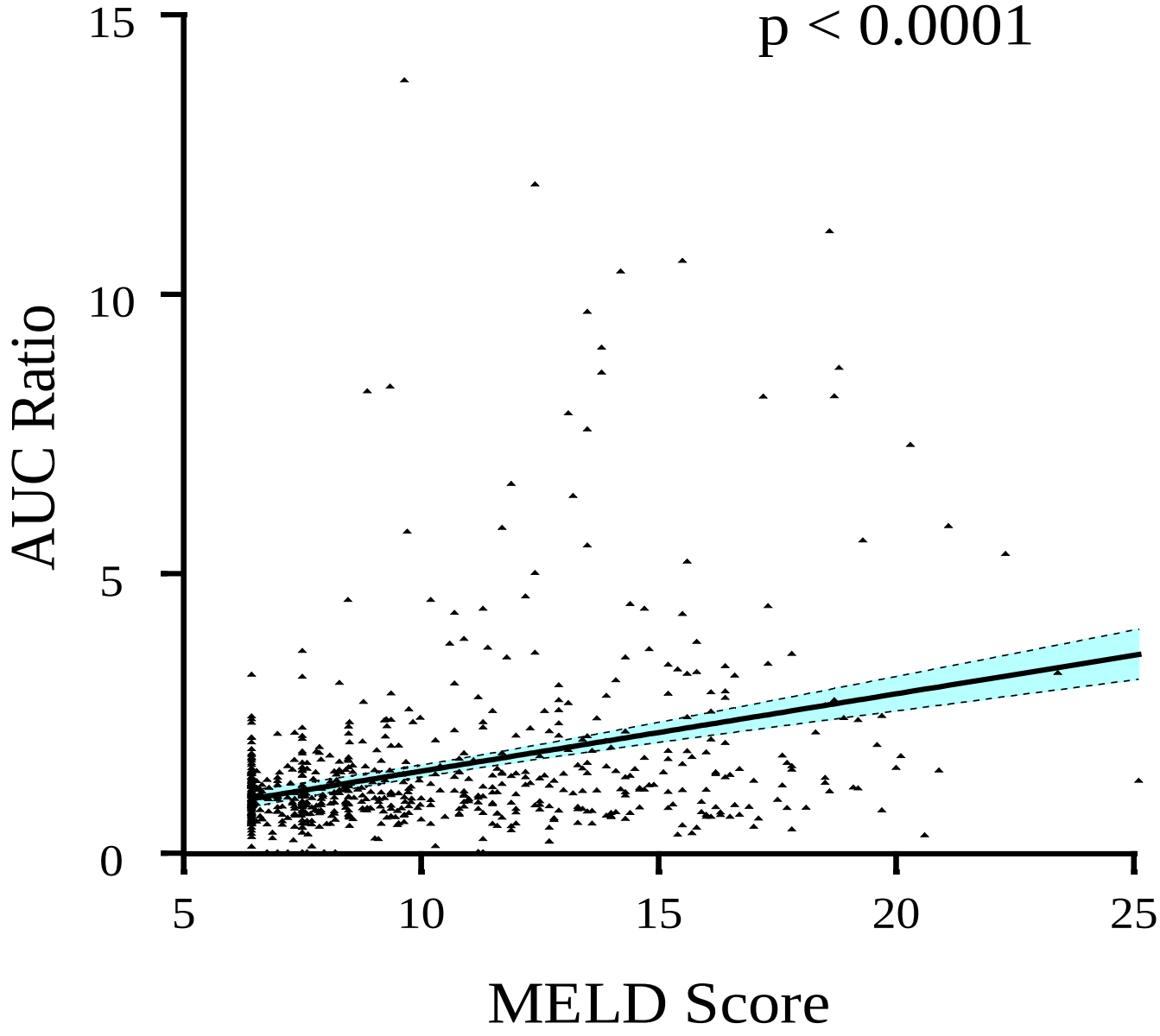
9.57 (ln Serum Creatinine] +

6.43


Cumulative Probability
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
AUC Ratio
<10
>10
MELD<10
MELD>10

Child-Pugh vs. MELD

	Child-Pugh Classification			
	Normal (N=240)	Mild (N=129)	Moderate (N=219)	Severe (130)
MELD < 10	98.3%	82.9%	46.1%	4.6%
MELD > 10	1.7%	17.1%	53.9%	95.4%

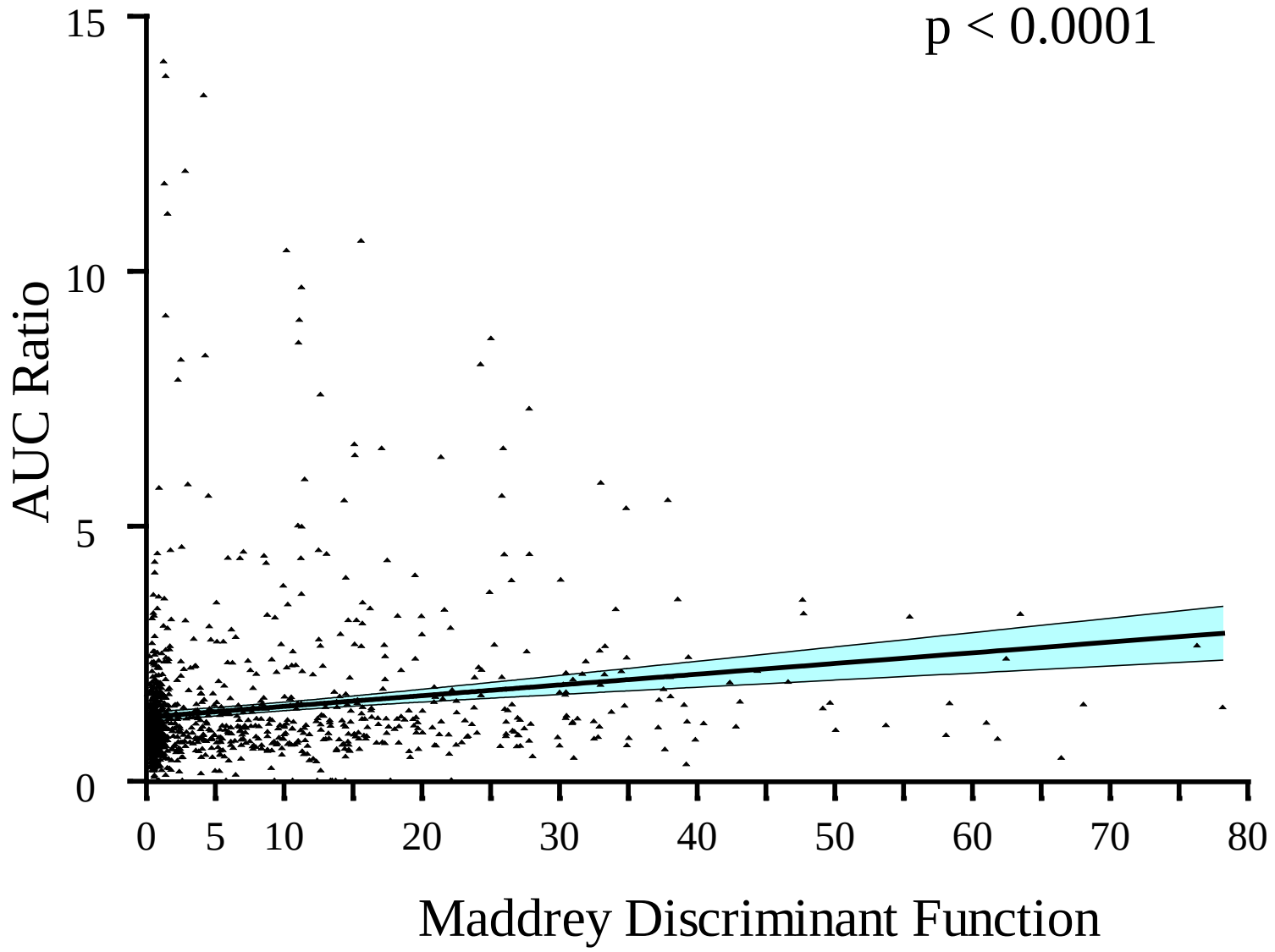

p < 0.0001
AUC Ratio
15
10
5
0
5
10
15
20
25
MELD Score

Maddrey Discriminant Function

Discriminant Function (df) =

4.6 * (Patient's Prothrombin Time, in seconds - Control Prothrombin Time in seconds) +

Serum Total Bilirubin, mg/dL


p < 0.0001
AUC Ratio
15
10
5
0
0
5
10
20
30
40
50
60
70
80
Maddrey Discriminant Function

Conclusion and Future Work

- NCI criteria appears to be the most sensitive liver function classification system for exposure changes.
- Cases where exposure changes as a function of liver impairment were not observed should be adjudicated to:
  - Understand drug characteristics that govern exposure changes with liver impairment
  - Explore ways to improve the sensitivity of liver impairment classification systems