Liver transplantation in primary cholestatic liver diseases

Transplant forum

19/1/2011

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Cholestatic indications for OLT

- Pediatric
  - Alagille syndrome
  - PFIC
  - Non-syndromic biliary hypoplasia
  - Nutrition related cholestasis
- Adult
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis

Indications for transplant

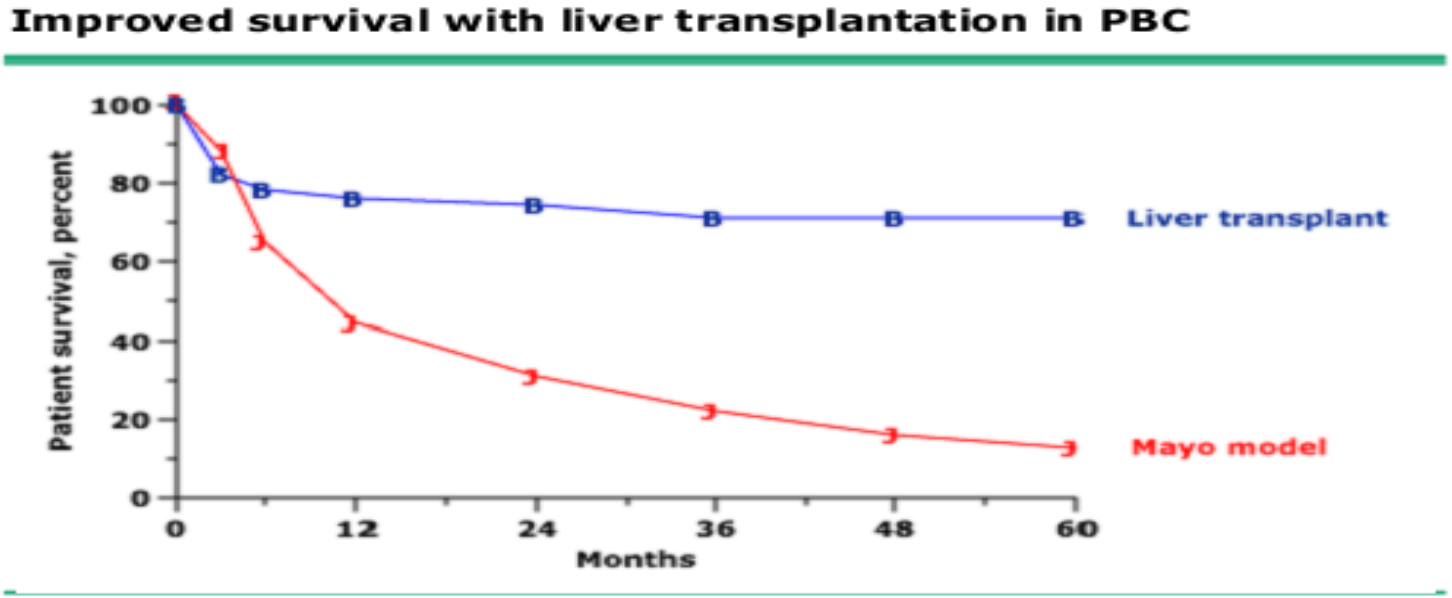
- Survival benefit: risk of death without Tx greater than risk with Tx
  - Generic models- MELD
  - Disease specific models- Mayo score
- Quality of life
  - √Intractable pruritis
    - Refractory to medical Rx (cholestyramine, refampicin, naltrexone etc.)
  - ?Recurrent, debilitating nontraumatic bone fractures
  - ?Recurrent episodes of cholangitis
  - XFatigue- not reversed with OLT. Try Modafinil
    - Goldblatt J et al. Gastroenterology. 2002 May;122(5):1235-41
    - Gross Cret al. Hepatology 1999;29:356–64

Timing of transplant

- Both MELD and Mayo scores superior to CTP for predicting mortality
  - Dickson ER et al. Hepatology 1989;10:1–7
  - Kamath PS et al. Hepatology 2001;33:464–70
  - Kim WR et al. Hepatology 1999;29;1643-1648
- No head to head comparison b/w MELD and Mayo
- MELD scores used in most programs
  - Underestimate disease severity in patients with primarily fatigue and pruritis- delay in Tx
  - Favor critically ill patient- poorer outcome, higher cost of Tx

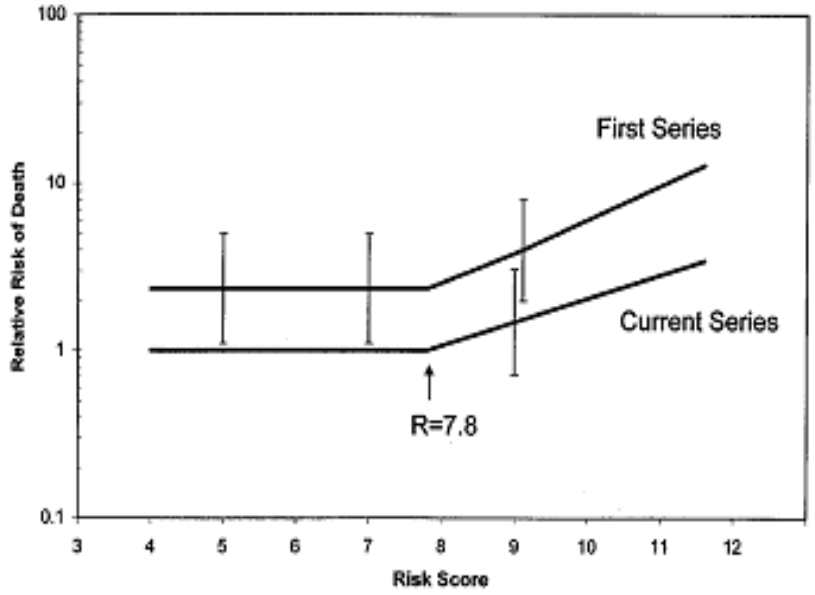
Mayo scores for OLT in PBC

- Based on bilirubin, albumin, age, edema, and PT
- OLT advised when 6m survival expected to be less than 80% (score ≈ 9.4, bilirubin >10mg/dl))
  - Markus BH et al. N Engl J Med 1989; 320:1709
  - Christensen E, et al. J Hepatol. 1999 Feb;30(2):285-92.



- Survival benefit of OLT evident 3-6m after Tx

- Earlier Tx may be beneficial with improved OLT survival currently
- Late transplant (R>7.8) leads to increased mortality and resource usage
  - Kim WR et al. Hepatology 1998;28:33–8

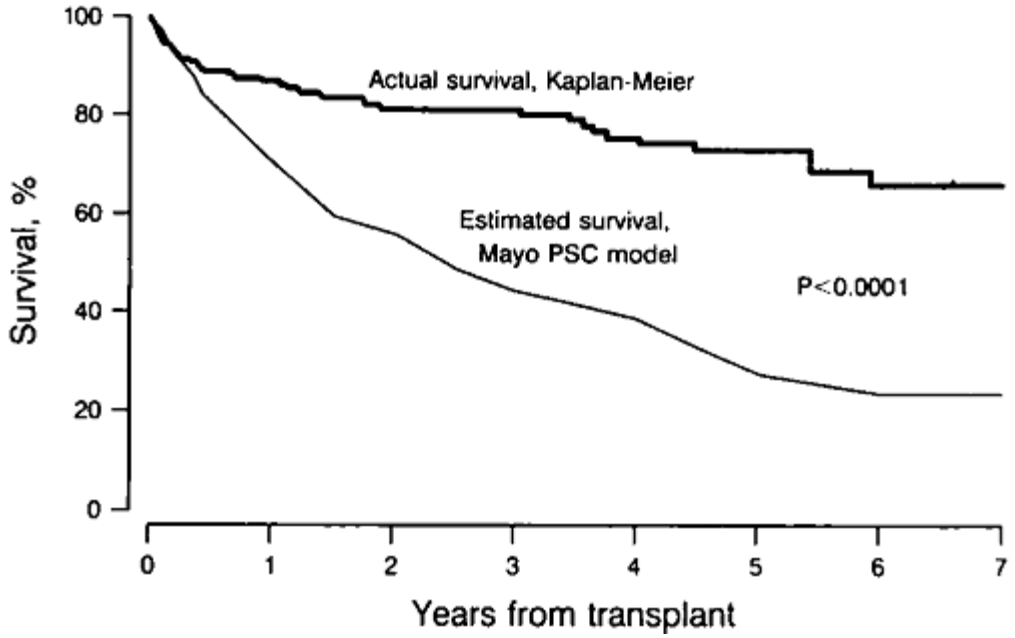


	Low Risk (R ≤ 7.8) (n = 82)	High Risk (R > 7.8) (n = 61)	P
LOS, Hospital (d)	16 (1-94)	19.5 (11-169)	.001
LOS, ICU (d)	3 (1-36)	4 (1-126)	.001
RBC (L)	1.3 (0.2-7.6)	2.2 (0.2-13.9)	.006

- OLT advocated when score between 6-7.8
  - Kim WR et al. Liver Transpl 2000; 6: 489-494

Mayo scores for OLT in PSC

- Based on age, bilirubin, albumin, AST and variceal bleed



- Similar to PBC: benefit evident 6m post Tx.
  - Abu-Elmagd KM et al.Surg Gynecol Obstet. 1993 Oct;177(4):335-44
- Tx when expected survival less than Tx survival for a given centre (Score of >2 used in Japan)
  - Tamura S et al. World J Gastroenterol 2008;14:5105-9

Results of OLT

Average life expectancy for male recipients by age group and primary liver disease

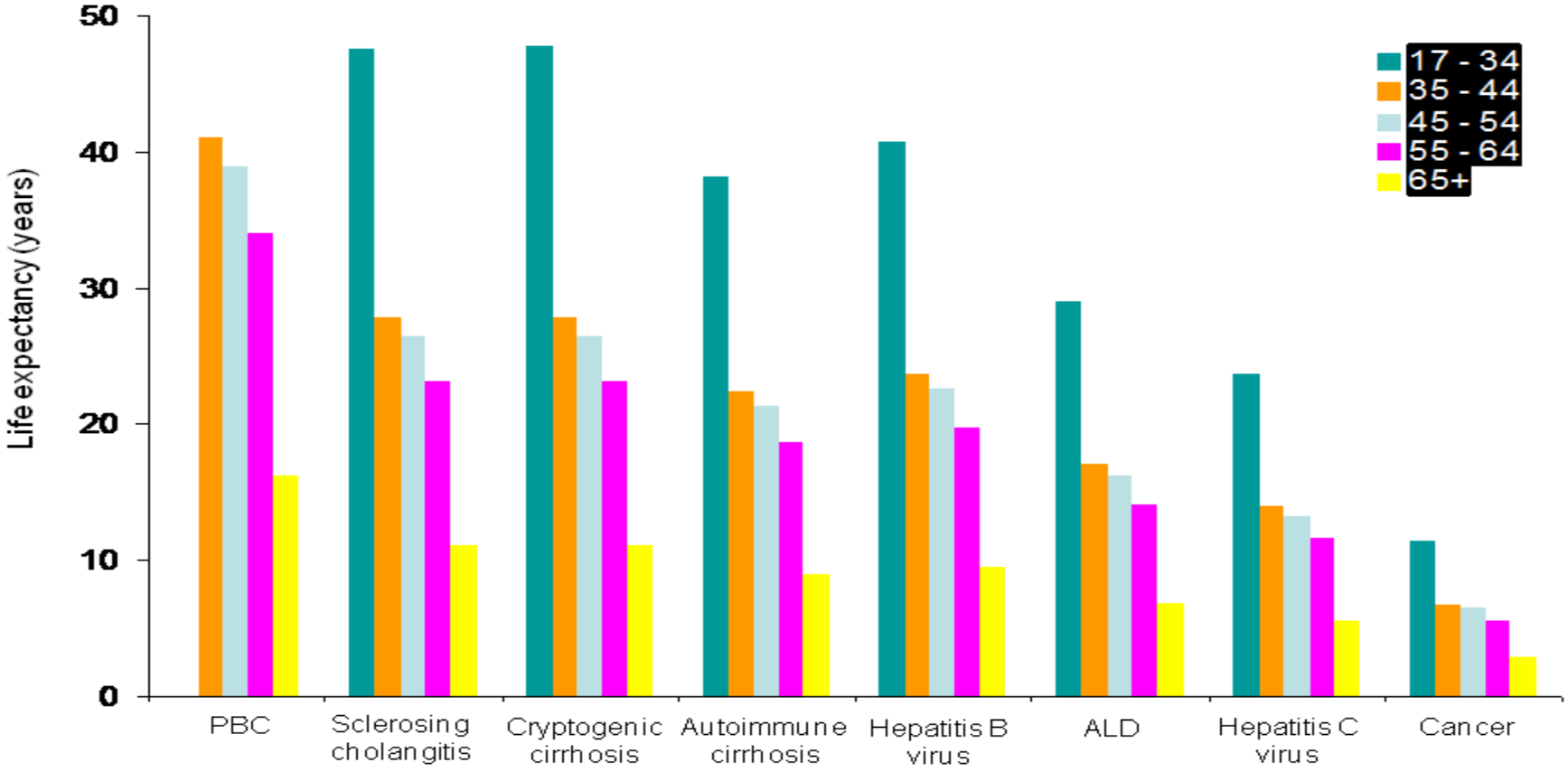


Table 4. Median Preoperative MELD Score and 1-Year Survival of Liver Transplant Recipients Analyzed by Principal Diagnosis

Median MELD Scores (Interquartile Range) and 1-Year Survival		Viral Liver Disease	Alcoholic Liver Disease	Cholestatic Liver Disease
United States	MELD score	15.6 (12.4–21)	16.7 (13.1–23.2)	16.1 (12.1–21.3)
	1-year survival (%)	86.8	88.2	92.9
Canada	MELD score	16.2 (12.1–20.8)	16.5 (13.5–22.8)	18.8 (14.1–21.7)
	1-year survival (%)	88.4	94.1	95.1
United Kingdom	MELD score	10.2 (8.4–13)	15.7 (12–20)	8.5 (7.5–11.1)
	1-year survival (%)	84.6	91.6	88

Abbreviation: MELD, model for end-stage liver disease.
Differences in MELD score within countries not significant except for the United Kingdom where cholestatic vs alcoholic liver disease (95% confidence interval of difference = −8.17 to −4.32) and viral vs alcoholic liver disease (95% confidence interval of difference = −6.69 to −2.77).

- Stell Da et al. Liver Transpl 2004;10:898–902

- 1, 5 and 10-year survival rates in PBC- 80-90%, 77%-88%, and 70-80%, respectively
  - Liermann Garcia RF et al. Hepatology 2001; 33:22
  - Hasegawa K et al. Transplant International 2005 ;18:794–799
- 1-year and 5-year survival rates of 90–97% and 80–85% respectively in PSC
  - Graziadei,I. W. et al. Hepatology 1999;30:1121–7
  - Wiesner R. H. Best Pract. Res. Clin. Gastroenterol 2001;15: 667–680

- Prompt reversal of pruritis, encephalopathy, UGI bleed and HRS
  - Gross CR et al. Hepatology 1999;29:356–64
- Jaundice and ascites resolve over weeks to months
- 12 -18 months for improvement in osteodystrophy
  - Eastell R et al. Hepatology 1996;14:296
- Fatigue responds poorly
  - Goldblatt J et al. Gastroenterology 2002; 22:1235-41
- ?Increase in IBD/Ca colon post Tx
  - Dvorchik I et al. Hepatology 2002; 35:380
  - Vera A et al. Transplantation 2003; 75:1983

Recurrence- PSC

- Mayo criteria

Inclusion criteria	Exclusion criteria
Confirmed diagnosis of primary sclerosing cholangitis prior to liver transplantation	Hepatic artery thrombosis/stenosis
Cholangiography: intrahepatic and/or extrahepatic biliary stricturing, beading and irregularities at least more than 90 days following transplantation	Established chronic ductopenic rejection
Histology: fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis or biliary cirrhosis	Anastomotic strictures alone
	Nonanastomotic strictures before posttransplantation day 90
	ABO incompatibility between donor and recipient

  - Graziadei IW et al. Hepatology 1999; 29:1050 –1056

- Difficult diagnosis:
  - May have normal LFT
  - Many causes of secondary cholangitis to be excluded
  - Histology/imaging not specific

- 1, 5, and10 years post-transplantation: 2, 12, and 20%
  - Campsen J et al. Liver Transpl 2008; 14:181
- Risk factors:
  - gender mismatch, male recipient
  - coexistent IBD, presence of an intact colon after Tx
  - Related LDLT
  - CMV infection, recurrent cellular rejection
  - use of OKT3, prolonged use of steroids
  - CCR5 Δ32 mutation, HLA-DRB1*08
    - Graziadei IW et al. Curr Opin Gastroenterol 2011;27:301–305
    - op den Dries S et al. Liver Int. 2011;31(8):1102-9

Recurrence- PBC

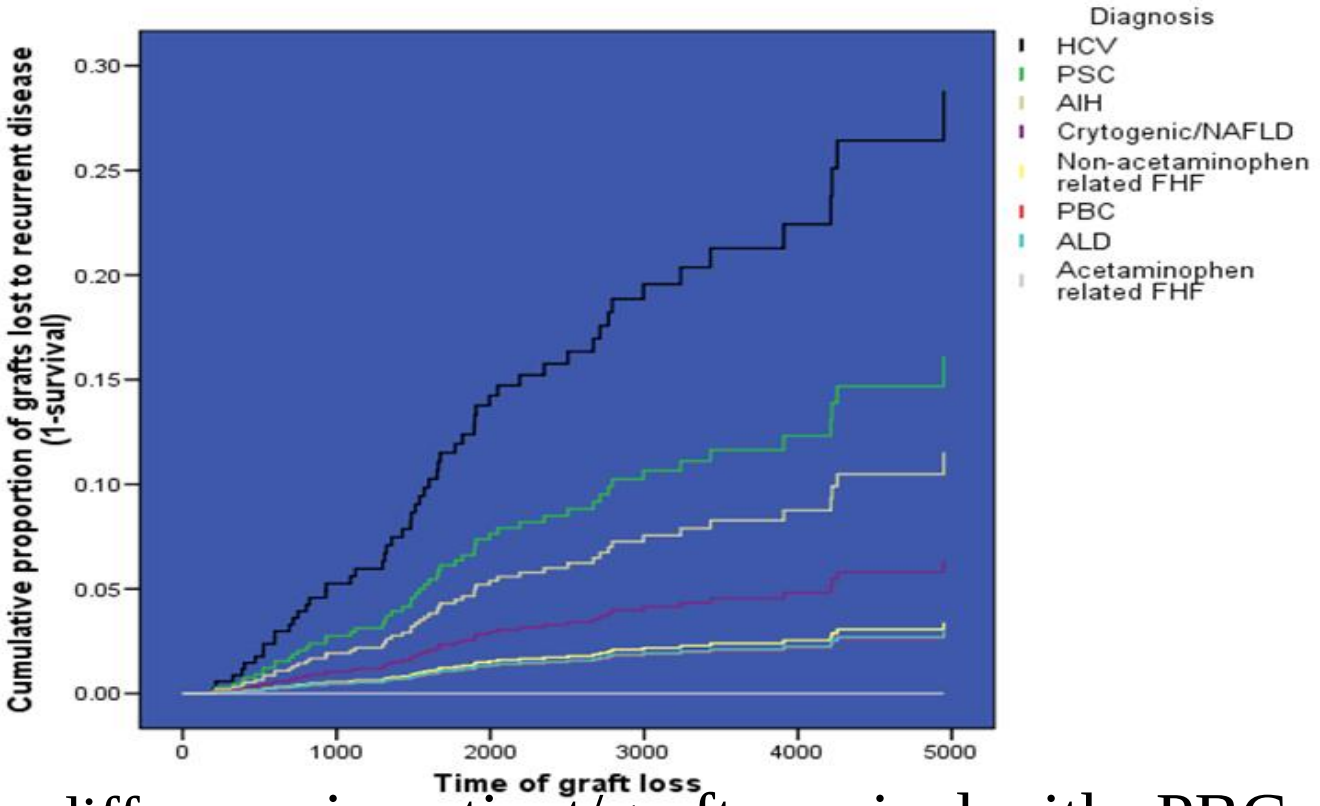
- Diagnostic criteria
  - Transplant for PBC **and**
  - Persistence of AMA **and**
  - Histology showing the characteristic portal tract lesions
    - Mononuclear inflammatory infiltrate
    - formation of lymphoid aggregates
    - epithelioid granulomas
    - bile duct damage
    - (3/4 for definite, 2/4 for probable)
      - Hubscher SG et al. J Hepatol 1993; 18:173
- LFT neither specific nor sensitive
- AMA titre/subtype not predictive
- Anti-GPC- non-specific, 100% sensitive for recurrence
  - Ciesek et al. Ann Hepatol 2010;9(2):181-5

- 8-18% at 5 year and 22-30% at 10 years
  - Liermann Garcia RF et al. Hepatology 2001; 33:22
  - Abu-Elamgd et al. Hepatology 1997; 26:176A

Recurrence of primary biliary cirrhosis after liver transplantation

Author	Year	No. of patients	Median follow-up after transplantation (mo)	Recurrence (%)	Median time to recurrence (mo)	Risk factors
Liermann-Garcia et al [8]	2001	400	56	17	36	Tacrolimus-based immunosuppression
Sanchez et al [54]	2003	156	72	11	50	—
Sylvestre et al [55]	2003	100	44	17	56	—
Neuberger et al [26]	2004	485	79	23	—	Tacrolimus-based immunosuppression
Jacob et al [25]	2006	100	118	14	61	Tacrolimus-based immunosuppression Recipient age
Charatcharoenwitthaya et al [23]	2007	154	—	34	—	Tacrolimus-based immunosuppression Male recipient

Impact of disease recurrence



- No difference in patient/graft survival with rPBC
  - Liermann Garcia RF et al. Hepatology 2001;33:22-7
  - Balan V. Surg Clin North Am. 1999;79:147-52
- rPSC may affect graft survival- controversial
  - Graziadei IW. Hepatology 1999;29:1050-6
  - Haga H et al. Hepatol Res 2007; 37 Suppl 3: S463-S469

Rx of recurrent disease

- Biliary dilatation for recurrent strictures in PSC
  - Difficult, may not be effective
- UDCA improves LFT but no effect on outcome in recurrent PBC
    - Charatcharoenwitthaya P et al. Liver Transpl. 2007;13:1236
- Retransplantation if significant graft dysfunction
  - Liermann Garcia RF et al. Hepatology 2001;33:22-7
  - Charatcharoenwitthaya P et al. Liver Transpl 2007;13:1236
  - Maheshwari A, et al. Am J Gastroenterol 2004;99:538–42
- Prevention of recurrence- no proven strategy
  - CyA instead of Tac
  - Slower steroid taper
  - UDCA

Conclusions

- Definite advantage of OLT vs. medical management in decompensated primary cholestatic diseases
- Tx when expected survival less that OLT survival/ intractable symptoms
- Results as good/better than other indications of OLT
- Disease recurrence not uncommon
- Difficult to diagnose without Bx
- Impact of recurrence on graft/patient survival minimal
- No definite Rx for recurrent disease- successful re-transplantation possible