Blood Group Incompatible Transplant in The Setting of Malignancy

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Introduction

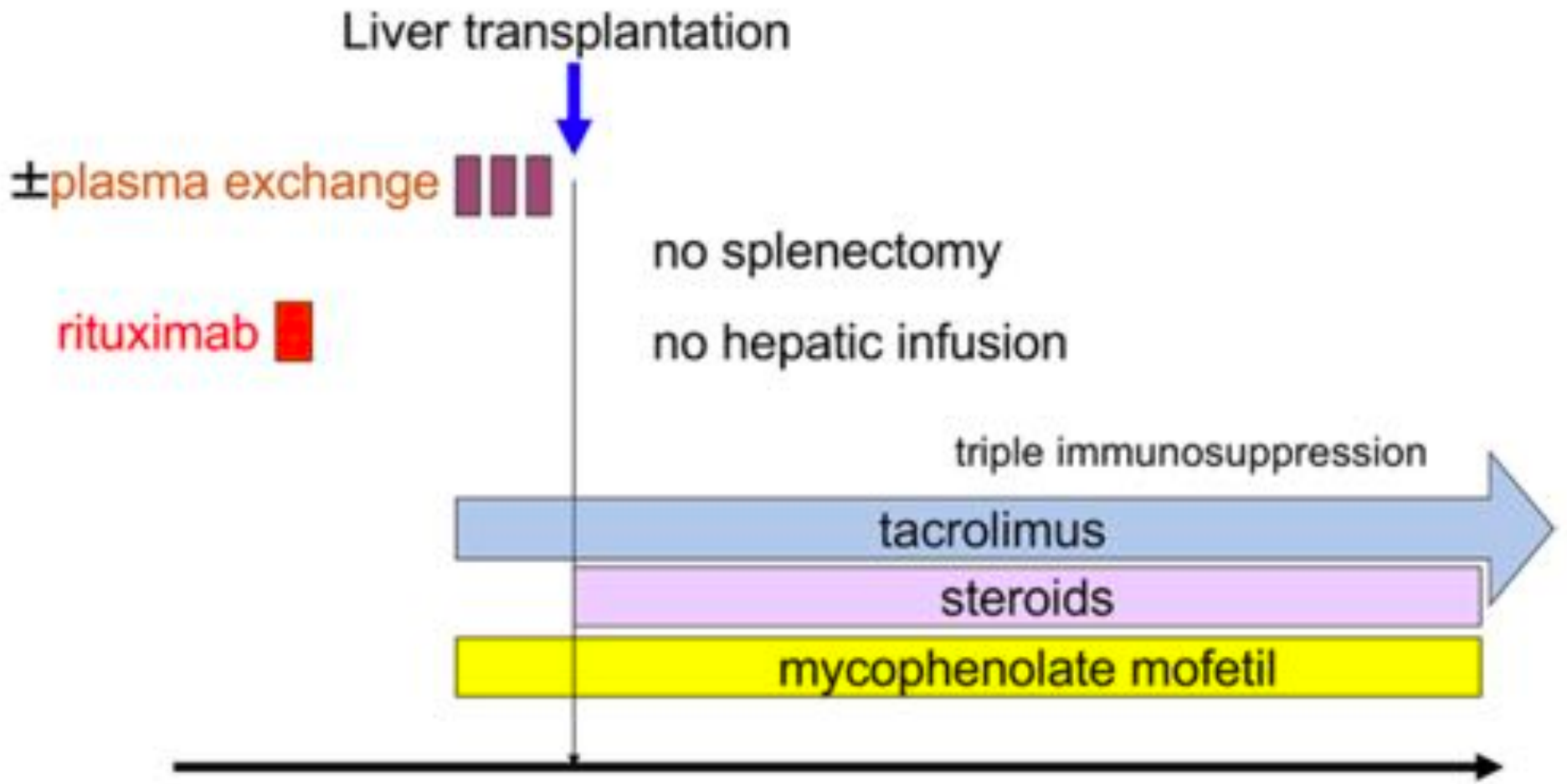
- In regions where liver grafts are scarce and donor rates are low, LDLT offers a timely alternative for eligible HCC patients with available living donors

- ABO-incompatible LT has becoming an additional alternative to ABO-compatible LDLT with much improved outcome due to effective desensitizing protocols, thus extending the recipient pool eligible for ABOi-LDLT

Desensitization Strategies for ABO-i Liver Transplantation

- Splenectomy
- Hepatic infusion strategy
  - PV infusion
  - HA infusion
- Extra-corporeal photopheresis (ECP)
- IVIG
- Plasma exchange/plasmapheresis
- B-cell targeted strategy
  - Rituximab

Current Standard Protocol for ABO-I Liver Transplantation



H Egawa et al. Transplantation 2023

Potent immunosuppression for ABOi Living Donor Renal Transplantation Not a Risk Factor for Malignancy

Retrospective study of 252 LDRT patients (Nagoya Daini Red Cross Hospital, Japan, 2003-2008)

Median FU 48 weeks

	ABO-Compatible (n = 189)	ABO-Incompatible (n = 63)	*P* Value
CNI (%)			
Cyclosporine	81.5	52.4	.0001*
Tacrolimus	18.5	47.6	.0001*
Antiproliferative (%)			
Mycophenolate mofetil	95.8	81.0	.0002*
Mizoribine	11.1	90.5	.0001*
Cyclophosphamide	0.0	90.5	.0001*

	ABO-Compatible	ABO-Incompatible
New onset of malignancy	8/189 (4.2%)	3/63 (4.8%)
Type of malignancy	Malingnant lymphoma: 2 Thyroid cancer: 2 Gastric cancer: 1 Renal cancer: 1 Uterus cancer: 1 Hepatic cancer: 1	Gastric cancer: 2 Malingnant lymphoma: 1

ABOI-recipients

- Splenectomy 2 weeks prior
- 4 sessions of double-filtration plasmapheresis
- Cyclophosphamide until 10 days post-op
- High-dose mizoribine (Mz) or MMF

Model	HR for Malignancy (95% CI, *P* Value)
Unadjusted	1.26 (0.33–4.75, 0.74)
Adjusted	1.43 (0.37–5.49, 0.60)[a]

*P <.05; [a]adjusted for donor age

T Yamamoto et al. Transpl Proc 2012

Cancer Risk After ABO-Incompatible Living-Donor Kidney Transplantation

- 318 living donor ABOi kidney recipients
  - 7 cancers identified with median diagnosis time 3.6 yrs (0.9-9.2)
  - NHL, Merkel cell carcinoma, gastric adenoca, HCC, papillary thyroid ca, pancreatic ca, and testicular germinoma

	ABOi	ABOc (entire cohort)	ABOc (matched controls)[a]
All cancers			
Rate[b]	7.1	8.5	7.1
IRR (95% CI) vs. entire cohort	0.86 (0.02–4.85)	Reference	
IRR (95% CI) vs. matched controls	0.99 (0.38–2.23)		Reference
NHL			
Rate[b]	1.0	1.2	1.0
IRR (95% CI) vs. entire cohort	0.76 (0.02–4.29)	Reference	
IRR (95% CI) vs. matched controls	1.02 (0.02–8.38)		Reference

[a] Matched 5:1 on age at transplantation (within 5 years), gender, race, zero HLA mismatch status, retransplantation, and year of transplantation (within 10 years) to ABOi recipients.
[b] Per 1000 person-years.

ABOi recipients had no difference in overall cancer risk compared with ABOc recipients in unadjusted ([IRR], 0.83; 95% [CI], 0.33,1.71; P=0.3) or matched (IRR, 0.99; 95% CI, 0.38,2.23) analyses

Single Center Retrospective Study on ABO-I Right Lobe LDLT

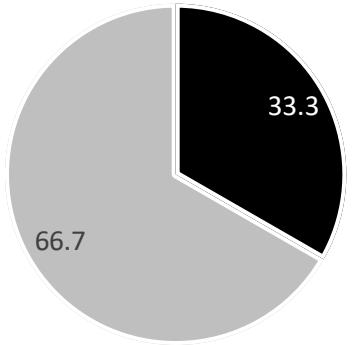
- **Consecutive patients with ABO-I Rt lobe LDLT at the National Cancer Center (Korea) between Jan 2012 – July 2013**

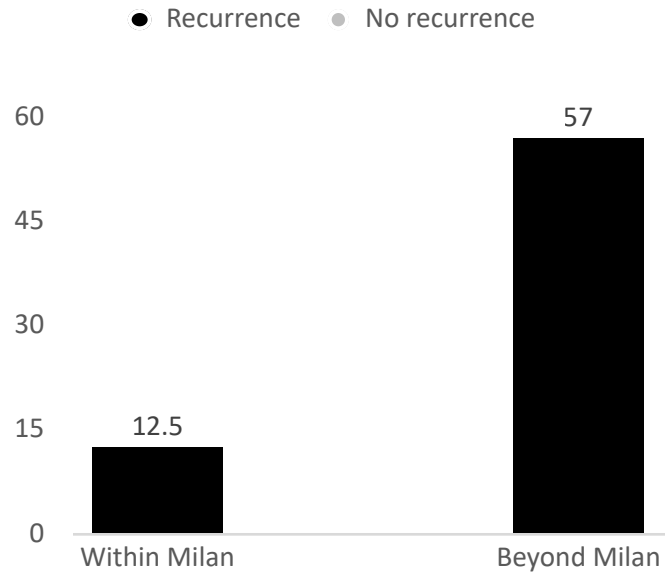
- ABO-I protocol
  - No splenectomy or local graft infusion therapy
  - Single dose of RTX (300 mg/m^2) 2 weeks before LDLT
  - PLEX sessions to decrease preformed anti-donor blood type isoagglutinin antibody titers to 1:16 1 week before LDLT
  - Basiliximab for induction therapy (20mg at D0 and D4)
  - High dose IVIG (0.8g/kg at D1 and D4)
  - High-dose steroid during the operation, followed by TAC and MMF with a combination of corticosteroid
    - Initial target TAC level ranged from 10 to 12 ng/mL and MMF started with 1.5 g/day.
    - Steroids were tapered to discontinuation by 6 months

Risk of Early HCC Recurrence in ABO-i Liver Transplantation

Consecutive ABO-I Rt lobe LDLT at National Cancer Centre (Korea) 2012-2013

Patients (n)	20
Age (years)	
Recipient	51.9 ± 8.6
Donor	36.7 ± 15.0
Sex (male/female)	
Recipient	14/6
Donor	10/10
MELD score	11.7 ± 4.4
Disease (HCC/liver cirrhosis)	15/5
Milan criteria (within/beyond)[a]	8/7
Viral infection (HBV/HCV/alcoholic)	15/1/4
ABO type (donor to recipient)	
A → B	3
A → O	5
B → A	3
B → O	3
AB → A	3
AB → B	3





SD Lee et al. Transpl Immunol 2015

Retrospective Study of ABO-I Adult LDLT for Patients with HCC from a Single Center

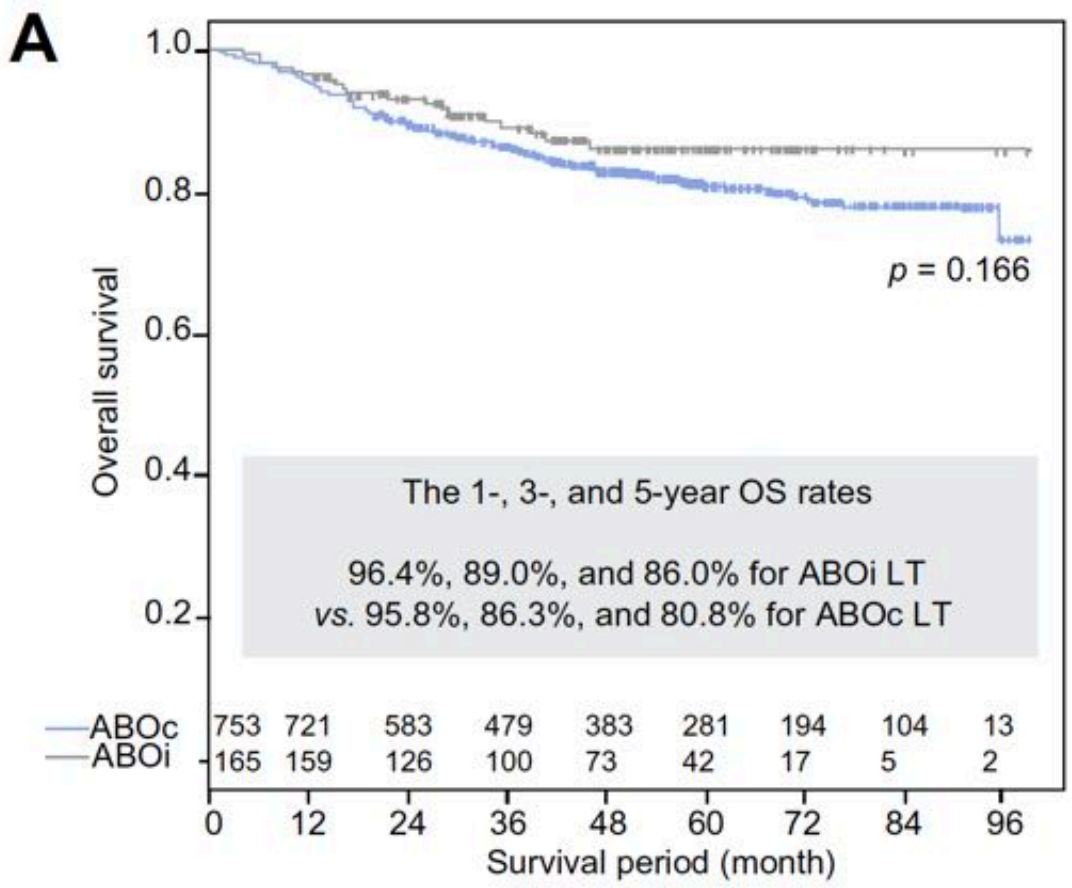
- **Retrospective reviewed 918 adult LDLT (Asan Medical Center, Seoul, Nov 2008-Dec 2015)**
  - 165 ABO-I LDLT for HCC
- Desensitizing protocol
  - RTX 2-3 weeks before LDLT
    - Nov 2008-Apr 2010: 375 mg/m2
    - After Apr 2010: 300 mg/m2
  - PLEX – to achieve antibody titer ≤1:8
- IV methylprednisolone (10 mg/kg) just prior to reperfusion
- Patients in the ABOi and ABOc groups used same IS regimen: TAC + MMF (500 mg bd), and steroids. Steroids were tapered over the three-month period

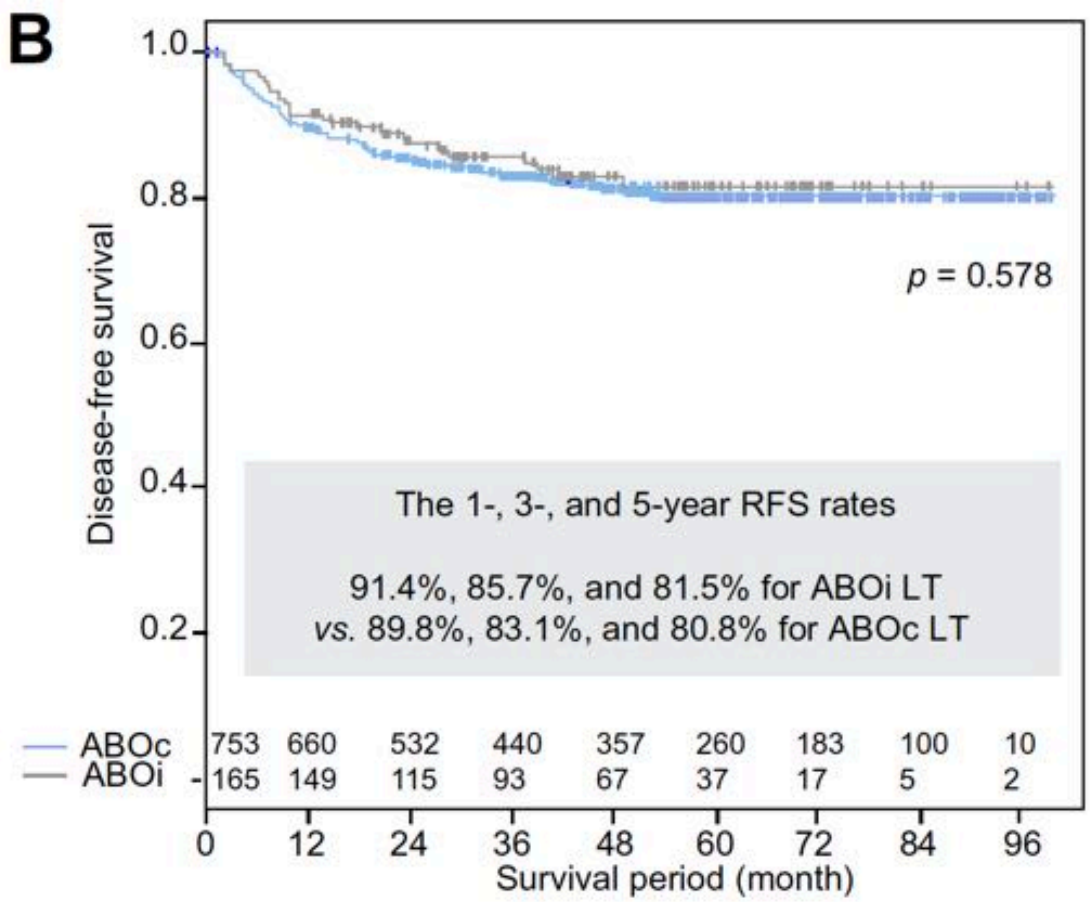
Comparison of Clinical Characteristics Between ABO-I vs. ABO-C Adult LDLT Recipients

Patients (n)	ABOi (n = 165)	ABOc (n = 753)	*p* value
Recipient			
Age (yr)	53.4 ± 7.0	54.1 ± 6.5	0.235
Gender, male	137 (83.0%)	650 (86.3%)	0.274
Time from HCC diagnosis to transplant (months)	24.9 ± 39.2	20.8 ± 28.9	0.133
Tumor characteristics, pretransplant			
Pre-LT HCC treatment	114 (69.1%)	566 (75.2%)	0.107
TACE	102 (61.8%)	513 (89.5%)	
Radiofrequency therapy	38 (23.0%)	166 (22.0%)	
Radiative therapy	6 (3.6%)	37 (4.9%)	
Hepatectomy	21 (12.7%)	89 (11.8%)	
HCC_number (n) by image	1.4 ± 1.8	1.8 ± 2.4	0.007
HCC_size (cm) by image	2.4 ± 2.6	3.3 ± 3.7	0.004
HCC_Max (cm) by image	1.7 ± 1.7	2.1 ± 1.7	0.006
Preop_AFP (ng/ml)	211.5 ± 1575.7	218.1 ± 1210.3	0.820
Unfulfilled Milan	29 (17.6%)	206 (27.4%)	0.009
Unfulfilled UCSF	25 (15.2%)	119 (15.8%)	0.835
Unfulfilled AMC	16 (9.7%)	63 (8.4%)	0.581

*HCC eligibility criteria (Asan): tumour size ≤5cm, tumour number ≤6, no gross vascular invasion. Even if beyond Asan criteria, may proceed to LT after downstaging

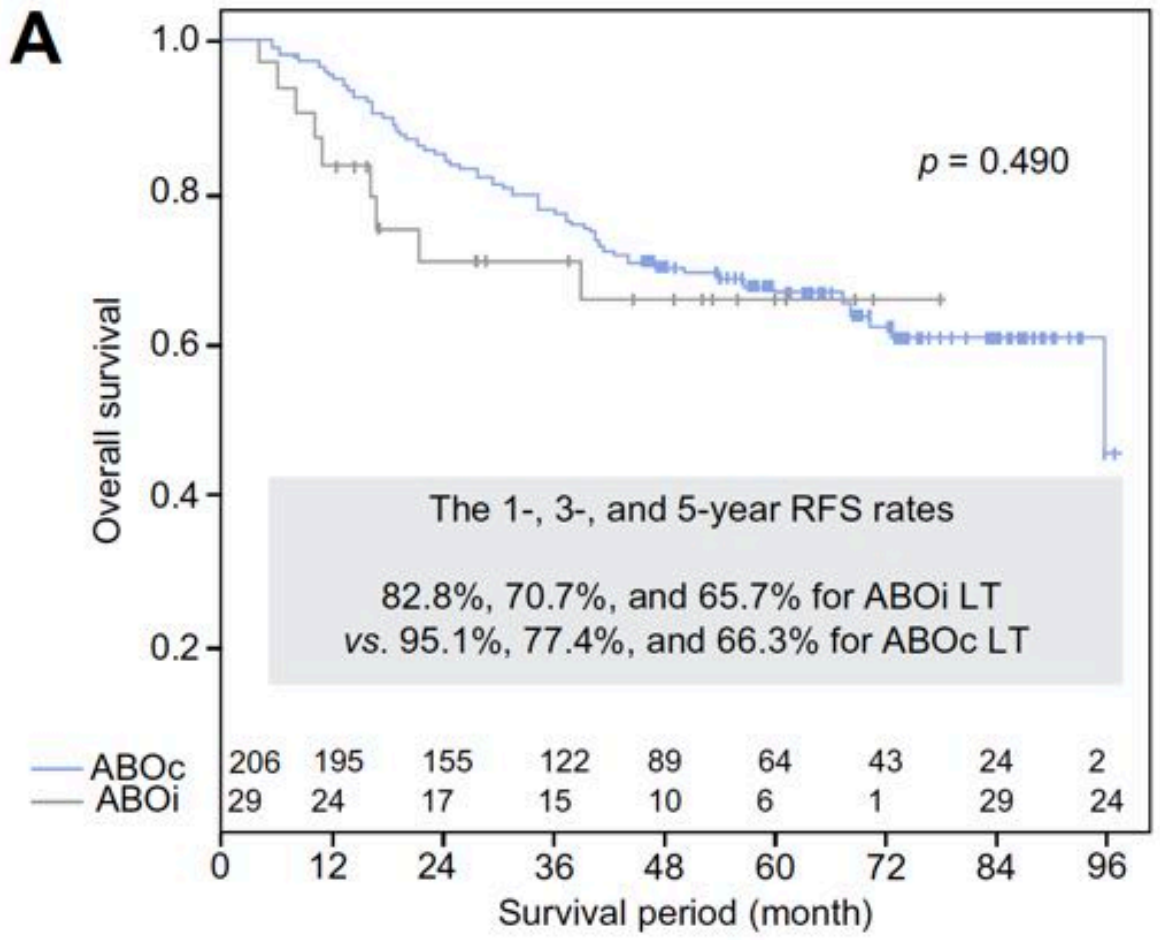
Overall and Recurrence-Free Survival After ABO-I Liver Transplantation for HCC (Entire Cohort)

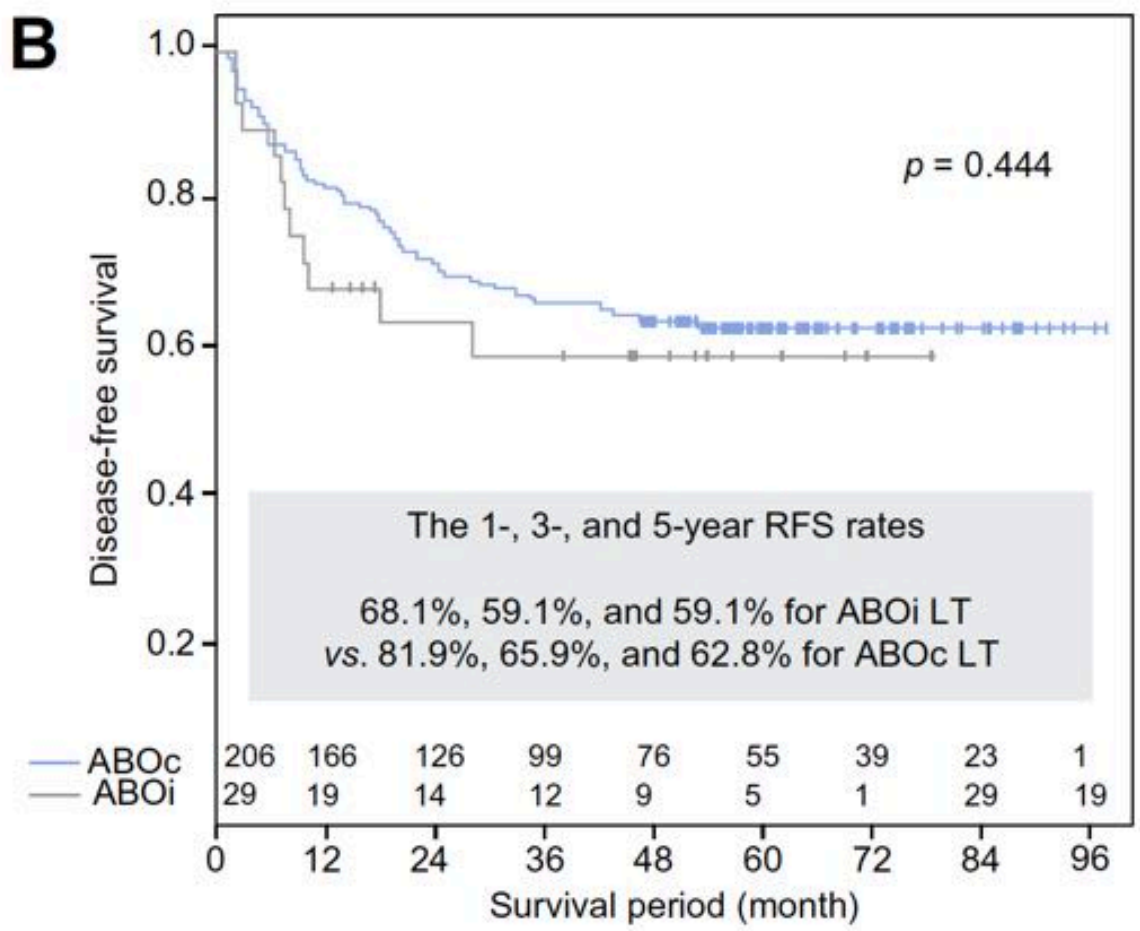




YI Yoon et al. J Hepatol 2018

Overall and Recurrence-Free Survival After ABO-I Liver Transplantation for HCC (Beyond Milan)





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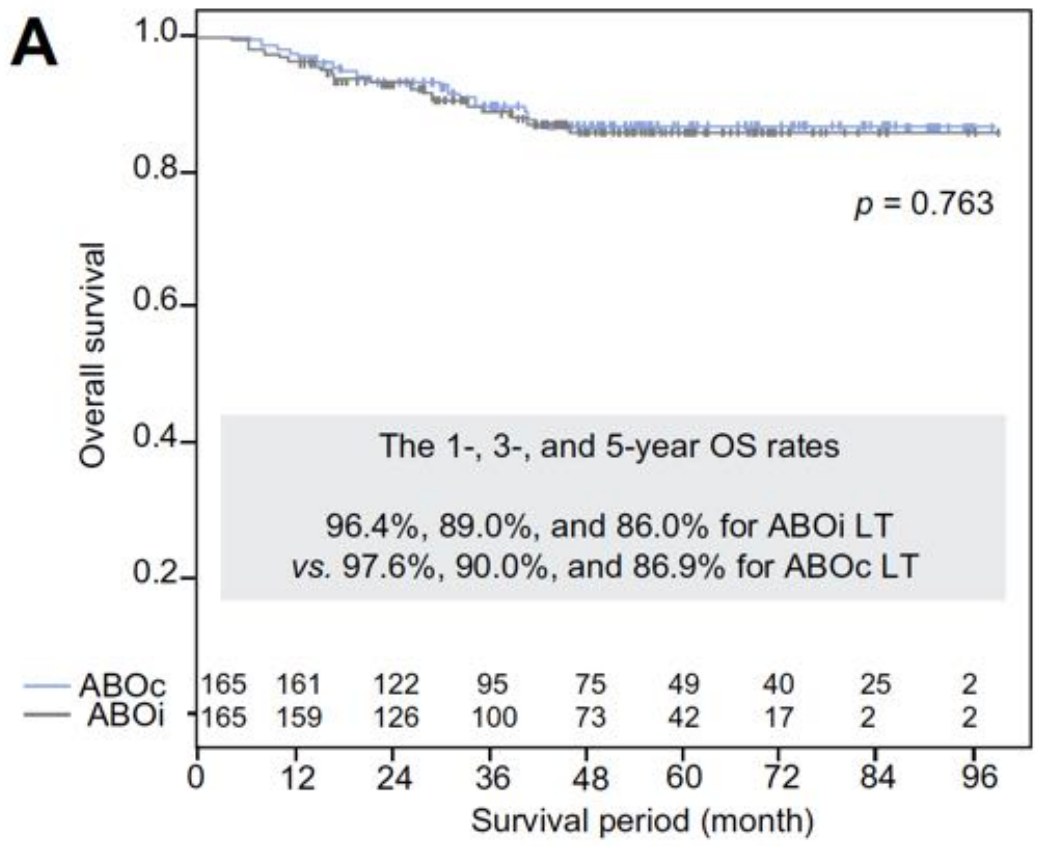
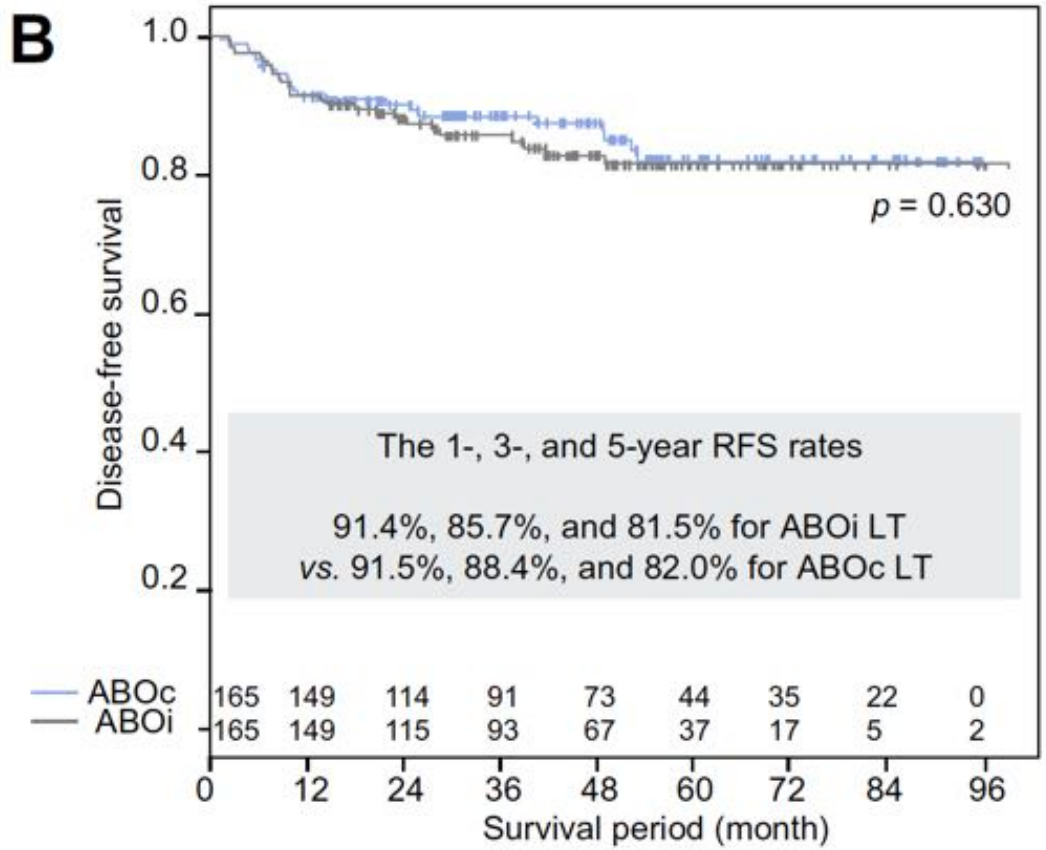
Overall and Recurrence-Free Survival After ABO-I Liver Transplantation for HCC (PSM Cohort)

Matched for age gender, etiology of cirrhosis, MELD, time from HCC Dx to LT, pre-LT locoregional Rx, HCC number, size, AFP, PIVKA II, unfulfilled Milan, unfulfilled UCSF, explant pathology characteristics





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Univariate & Multivariate Analysis of Risk Factors for HCC Recurrence

DFS	Univariate		Multivariate	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
ABO-incompatible	0.71 (0.44–1.15)	0.166	1.12 (0.74–1.71)	0.593
Recipient sex (male)	0.59 (0.35–1.01)	0.052		
Recipient age	0.99 (0.97–1.01)	0.369		
MELD score	0.98 (0.95–1.01)	0.121		
Pre-LT HCC treatment	1.84 (1.22–2.78)	0.004	1.95 (1.28–2.97)	0.002
Preop_AFP >50 ng/ml	2.46 (1.79–3.39)	0.000		
Preop PIVKA_II >40 mAu/ml	2.55 (1.87–3.49)	0.000	1.73 (1.25–2.39)	0.001
PET, hypermetabolism	2.82 (2.06–3.86)	0.000	1.70 (1.22–2.38)	0.002
Unfulfilled Milan	3.45 (2.53–4.71)	0.000	1.56 (1.09–2.23)	0.014
Unfulfilled UCSF	2.84 (2.04–3.96)	0.000		
Unfulfilled AMC	3.29 (2.25–4.81)	0.000		
Pathology of HCC on explant liver				
Total sum of existing HCC diameters	1.12 (1.09–1.16)	0.000		
HCC, maximum diameters	1.29 (1.22–1.37)	0.000		
HCC_number	1.09 (1.06–1.12)	0.000		
Lymphovascular invasion	7.35 (5.36–10.1	0.000	5.07 (3.57–7.19)	0.000
Necrosis (%)				
0–30	2.50 (1.65–3.79)	0.000		
>30	1.37 (0.96–1.97)	0.083		

ABO-I was not a risk factor for HCC recurrence in the univariate or multivariate analysis

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Single Center Retrospective Study of HCC LDLT Recipients

- 253 adult HCC patients with LDLT at Samsung Medical Center (Seoul, Sep 2010-June 2015)
- Desensitizing protocol for ABO-I LT
  - Single IV RTX dose 375 mg/m2 2 weeks before LDLT
  - PLEX every other day for 1-2 weeks before LDLT until titers of IgM and IgG isoagglutinin for donor ABO blood group ≤1:16
- Basiliximab 20mg at induction for all LDLT + D4
- All patients infused with PGE1, gabexate mesilate, and methylpred
- Maintenance IS: corticosteroids, TAC, and MMF. Corticosteroids withdrawn after 3 months

Baseline Characteristics of ABO-C and ABO-I Adult LDLT

	ABO-C (n = 181)	ABO-I (n = 59)	P
Donor			
Sex (male)	129 (71.3%)	39 (66.1%)	0.51
Age, y	29 (18-62)	31 (18-68)	0.52
Recipient			
Sex (male)	160 (88.4%)	53 (89.8%)	0.76
Age, y	55 (37-77)	56 (33-67)	0.52
Etiology			0.08
HBV	147 (81.2%)	54 (91.5%)	
HBV, HCV	0 (0%)	1 (1.7%)	
HCV	18 (9.9%)	1 (1.7%)	
NBNC	8 (4.4%)	1 (1.7%)	
Alcoholic	8 (4.4%)	2 (3.4%)	
Child-Pugh class			0.96
A	108 (59.7%)	35 (59.3%)	
B	53 (29.3%)	18 (30.5%)	
C	20 (11.1%)	6 (10.2%)	
MELD score	10 (6-46)	10 (6-35)	0.95

Tumour Characteristics of ABO-C and ABO-I Adult LDLT

	ABO-C (n = 181)	ABO-I (n = 59)	P
Pretransplant			
Locoregional therapies	133 (73.5%)	39 (66.1%)	0.32
TACE	122 (67.4%)	37 (62.7%)	0.53
No. TACE	3 (1-18)	4 (1-17)	0.24
RFA	46 (25.4%)	17 (28.8%)	0.61
No. RFA	1 (1-7)	2 (1-7)	0.02
Radiation	13 (7.2%)	7 (11.9%)	0.28
Operation	38 (22.5%)	10 (17.5%)	0.33
AFP >35 ng/mL	68 (37.6%)	15 (25.4%)	0.16
PIVKA-II (mAU/mL) (n = 64)	26 (4-22462) (n = 48)	31 (12-3358) (n = 16)	0.17
Explant liver			
Maximum tumor size (cm)	2.5 (0.5-11.0)	2.8 (0.8-11.0)	0.67
Tumor number	1 (1-14)	2 (1-16)	0.35
Milan criteria			0.94
Within	131 (72.4%)	43 (72.9%)	
Beyond	50 (27.6%)	16 (27.1%)	
Encapsulation	126 (78.3%)	48 (87.3%)	0.17
Microvascular invasion	90 (56.3%)	29 (52.7%)	0.75
Portal vein tumor thrombosis	11 (6.9%)	3 (5.5%)	0.71
Bile duct tumor thrombosis	6 (3.8%)	2 (3.6%)	0.96
Intrahepatic metastasis	55 (34.6%)	15 (27.3%)	0.41
Multicentric occurrence	55 (34.6%)	18 (32.7%)	0.87

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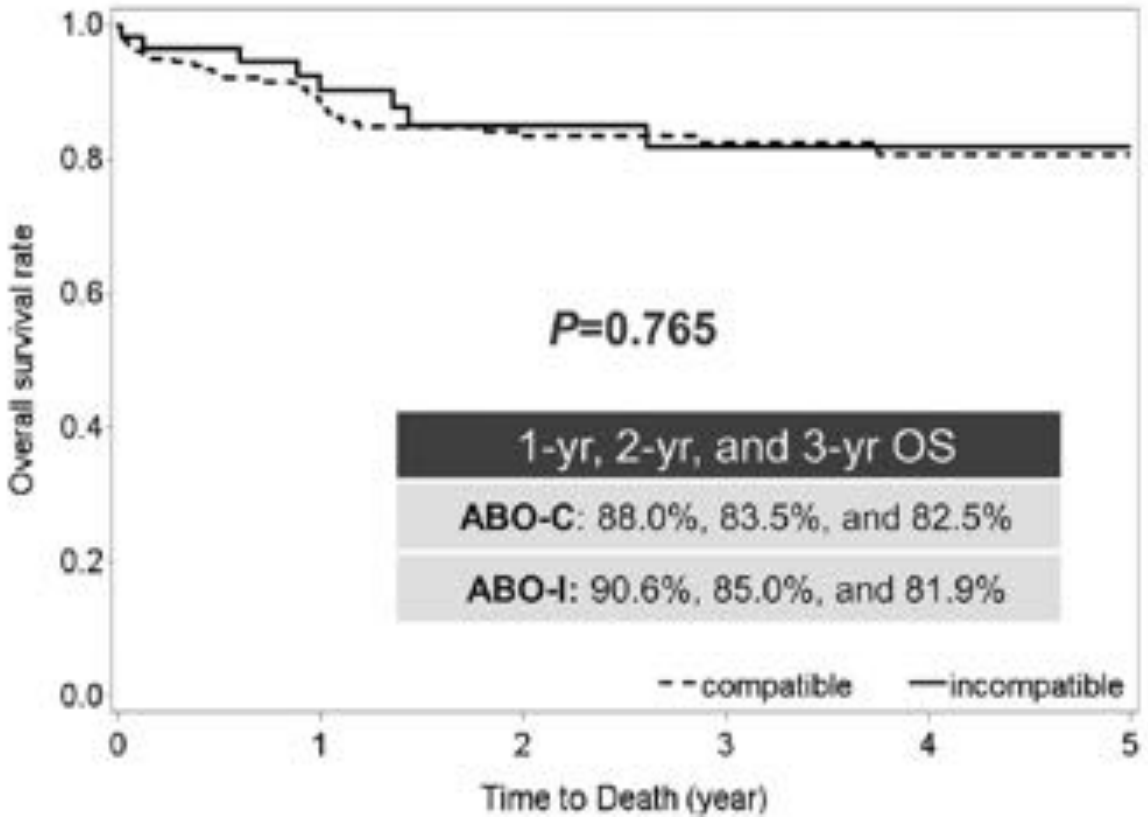
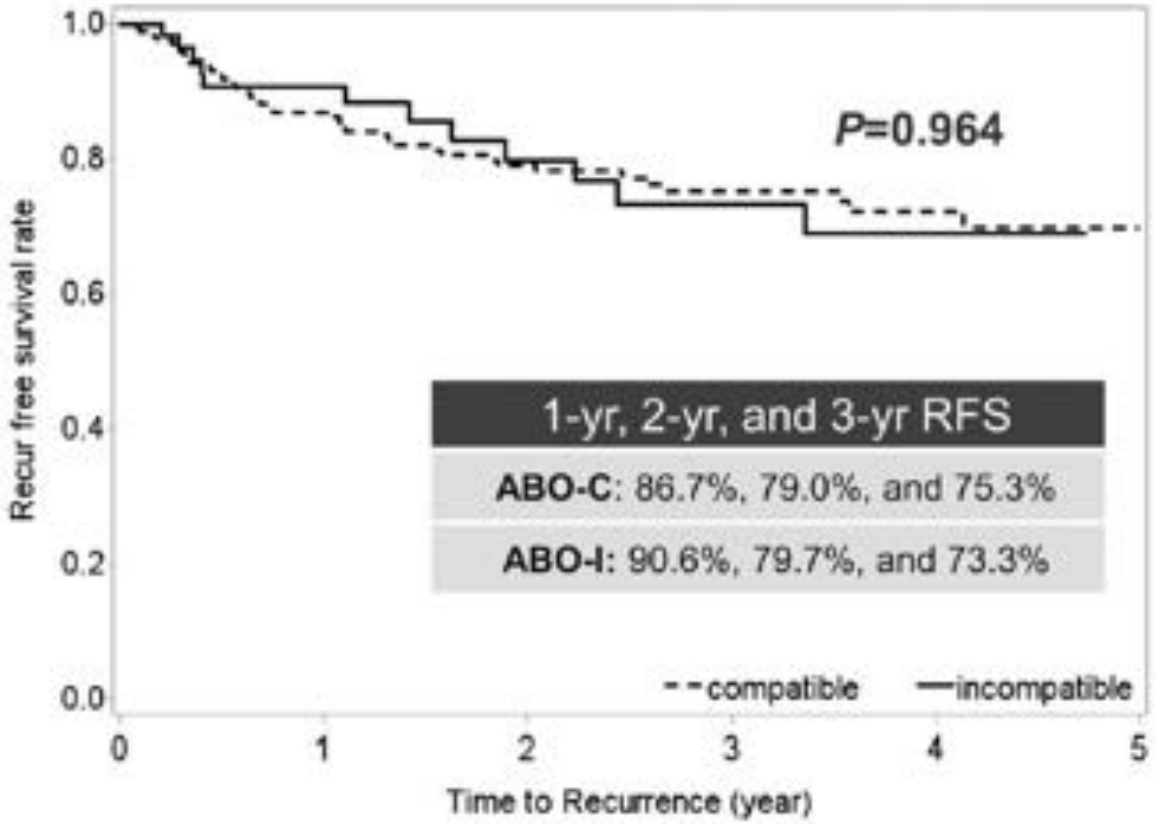
Overall and Recurrence-Free Survival Between ABO-C and ABO-I LDLT for HCC

Overall Survival



Disease-Free Survival



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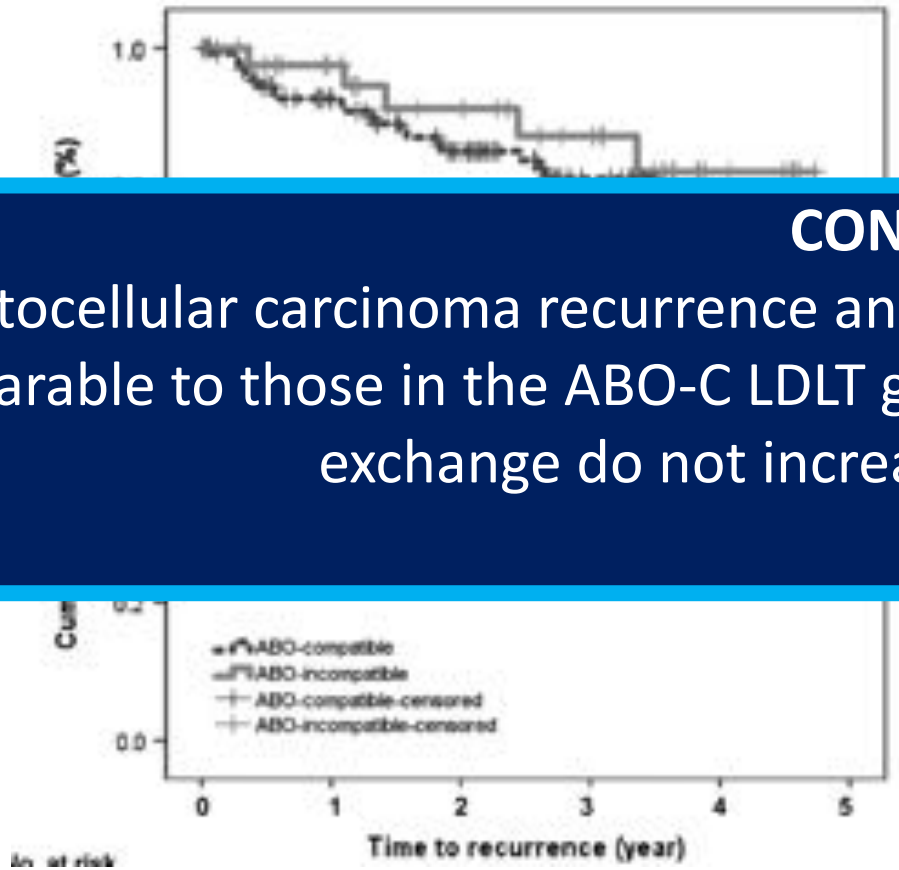
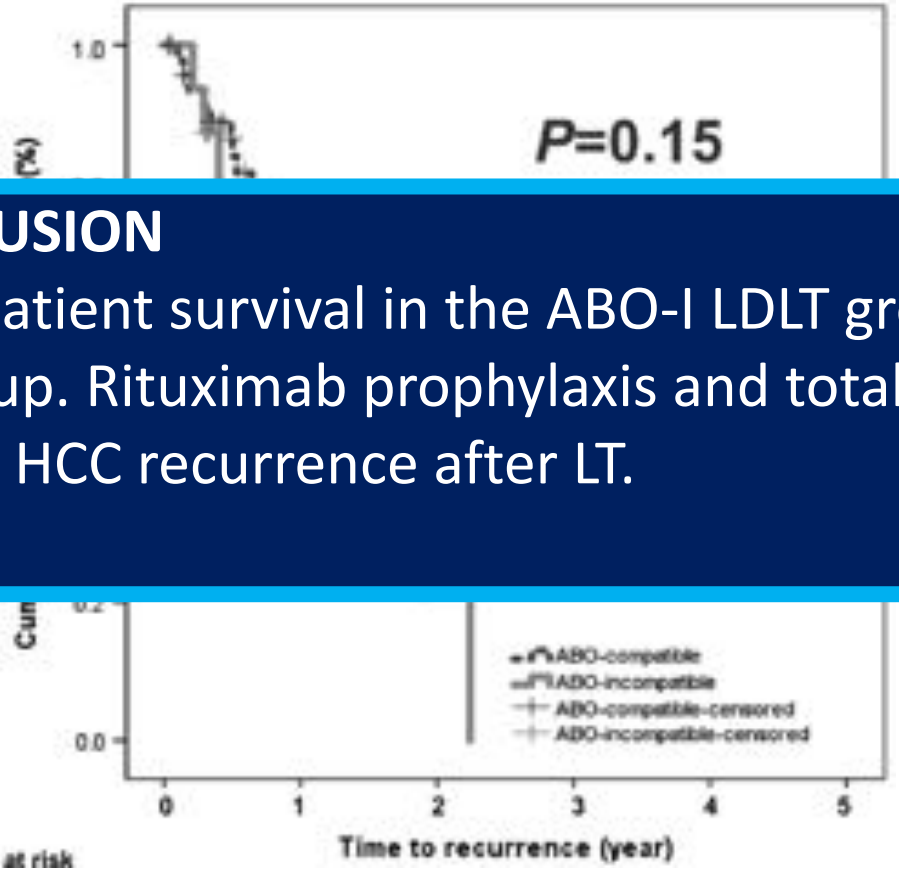
Disease-Free Survival Between ABO-C and ABO-I LDLT According to Milan Criteria

Within Milan



Beyond Milan



CONCLUSION

Hepatocellular carcinoma recurrence and patient survival in the ABO-I LDLT group are comparable to those in the ABO-C LDLT group. Rituximab prophylaxis and total plasma exchange do not increase HCC recurrence after LT.

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Single Center Study on Impact of ABO-I on HCC Recurrence After LDLT

- **Consecutive patients with ABO-I Rt lobe LDLT at the National Cancer Center (Korea) between Jan 2012 – Dec 2015**
- HCC ABO-I LDLT patients randomly matched by 1:2 ratio to ABO-C LDLT during same period according to propensity score
- Desensitizing protocol
  - Single dose IV RTX 300mg/m2 before LDLT
  - IVIG 0.8g/kg D1-4
  - PLEX prior to March 2014 – stopped after
  - No splenectomy, graft local infusion, pre-op MMF
- Basiliximab 20mg at induction + D4
- Maintenance: TAC, MMF (1.5g/d), corticosteroids (tapered off within 6m)

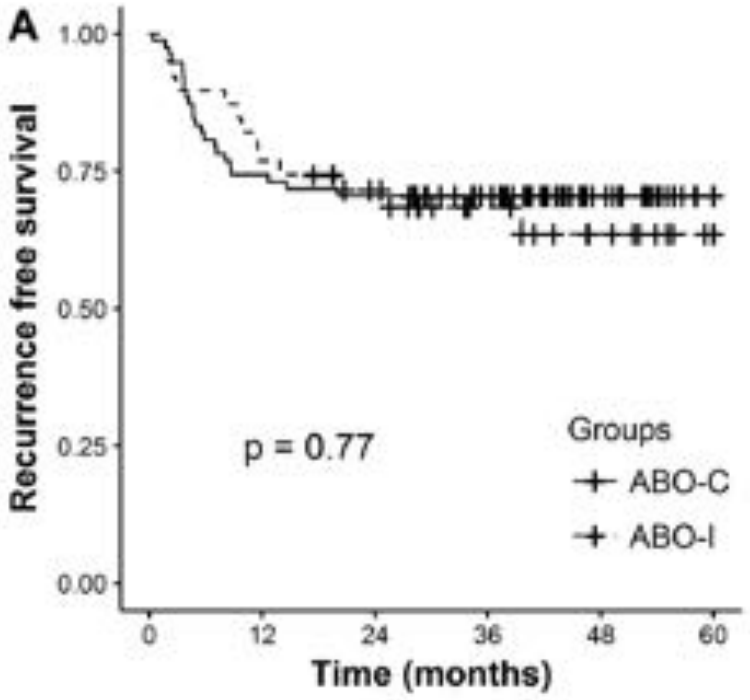
SH Kim et al. Eur J Surg Oncol 2019

Baseline Characteristics of Propensity-Matched Groups

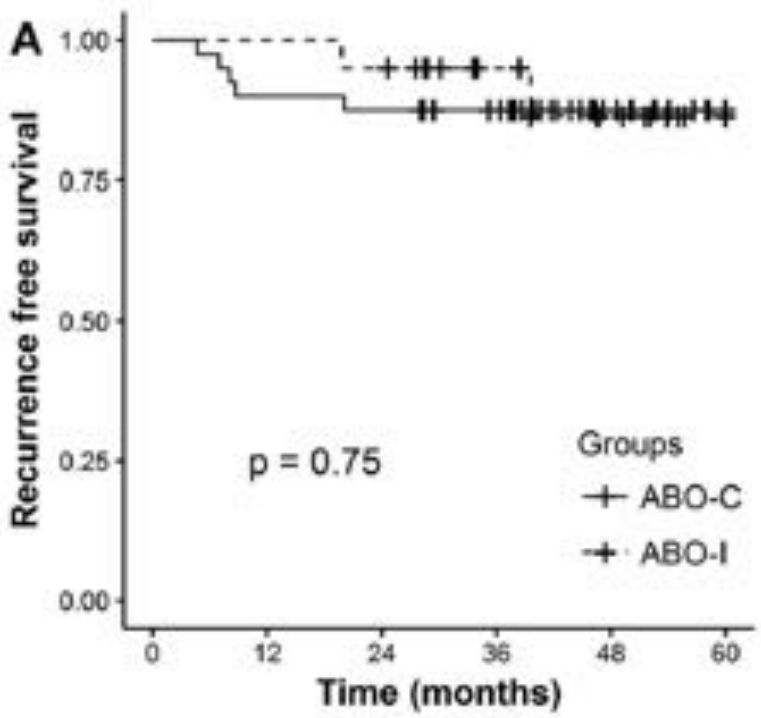
Characteristics	ABO-C (N = 78)	ABO-I (N = 39)	Total (N = 117)	P
Age (years)				
Recipient	55 (51–61)	54 (51.5–57.5)	55 (51–60)	0.48
Donor	32 (23–43)	31 (23.5–48.5)	32 (23–46)	0.79
Sex (male/female)				
Recipient	59 (75.6)/19 (24.4)	27 (69.2)/12 (30.8)	86 (73.5)/31 (26.5)	0.60
Donor	48 (61.5)/30 (38.5)	24 (61.5)/15 (38.5)	72 (61.5)/45 (38.5)	>0.99
Viral status (HBV/HCV/both/none)	65 (83.3)/3 (3.8)/2 (2.6)/8 (10.3)	33 (84.6)/0 (0.0)/0 (0.0)/6 (15.4)	98 (83.8)/3 (2.6)/2 (1.7)/14 (12.0)	0.38
Child-Pugh score	5 (5–7)	6 (5–7)	6 (5–7)	0.39
MELD score	10 (8–13)	10 (8–13)	10 (8–13)	0.90
AFP (ng/mL)	11.6 (4.0–220.3)	15.4 (5.4–192.6)	11.7 (4.8–220.3)	0.83
Operation time (min)				
Recipient	384 (343–429)	379 (340–429)	383 (343–429)	0.99
Donor	166 (146–184)	165 (147–189)	165 (146–184)	0.85
Cold ischemic time (min)	86 (71–102)	80 (71–105)	86 (71–103)	0.69
Warm ischemic time (min)	20 (17–24)	21 (16–24)	20 (17–24)	0.76
EBL (ml)	1200 (600–2500)	1500 (700–2600)	1300 (700–2500)	0.65
GRWR	0.97 (0.72–1.23)	0.97 (0.80–1.21)	0.97 (0.74–1.21)	0.75
Graft fatty change (%)	5.0 (0.0–10.0)	5.0 (0.0–17.5)	5.0 (0.0–10.0)	0.74
Number of tumors	2 (1–4)	2 (1–4)	2 (1–4)	0.35
Largest tumor size (cm)	2.2 (1.5–3.5)	2.5 (1.8–3.5)	2.2 (1.5–3.5)	0.36
Edmond-Steiner grade (I/II/III/IV)	4 (5.1)/13 (16.7)/42 (53.8)/19 (24.4)	1 (2.6)/9 (23.1)/16 (41.0)/13 (33.3)	5 (4.3)/22 (18.8)/58 (49.6)/32 (27.4)	0.46
Major vessel invasion (no/yes)	72 (92.3)/6 (7.7)	34 (87.2)/5 (12.8)	106 (90.6)/11 (9.4)	0.58
Microvascular invasion (no/yes)	50 (64.1)/28 (35.9)	24 (61.5)/15 (38.5)	74 (63.2)/43 (36.8)	0.95
T Stage (AJCC 7th) (1/2/3/4)	15 (19.2)/45 (57.7)/13 (16.7)/5 (6.4)	11 (28.2)/21 (53.8)/7 (17.9)/0 (0.0)	26 (22.2)/66 (56.4)/20 (17.1)/5 (4.3)	0.32

Comparable Survival of ABO-I vs. ABO-C Liver Transplantation for HCC

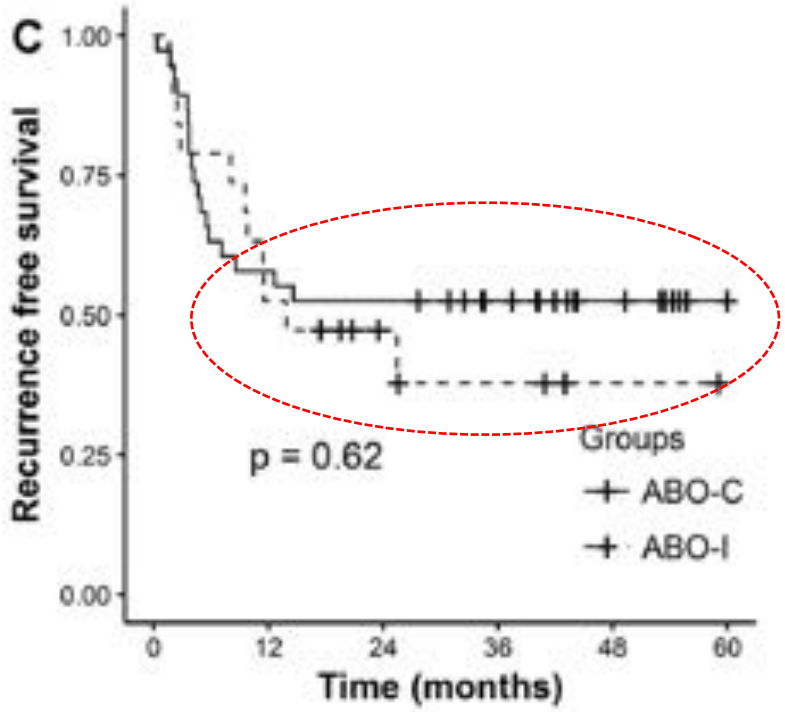
Overall



Within MC



Beyond MC



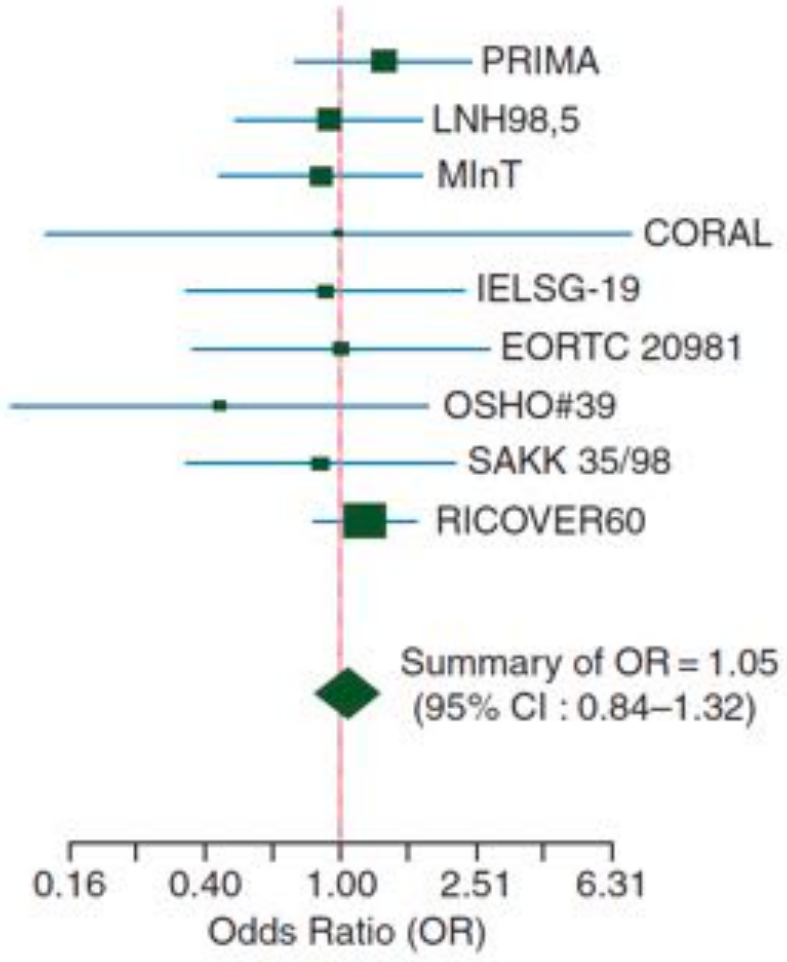
No adverse impact of ABO-incompatibility on oncological outcomes following LDLT for HCC by showing no significant differences in recurrence and patient survival between ABO-I and ABO-C LDLT patients with HCC

ABO-I LDLT can be considered a feasible choice of treatment for HCC patients awaiting LT with no compatible donor

SH Kim et al. Eur J Surg Oncol 2019

Risk of Rituximab in Secondary Malignancies

- RTX is a murine/human chimeric anti-CD20 monoclonal antibody that causes B-cell death by targeting the CD20 surface protein
- Profound normal B-cell depletion for several months
  - Reduction in T-cell activation
  - Reduced cancer immunosurveillance
- Meta-analysis of 9 RCT (n=4621) with median FU 73 months
  - Non-Hodgkin's lymphoma
  - No increase risk in second primary malignancy

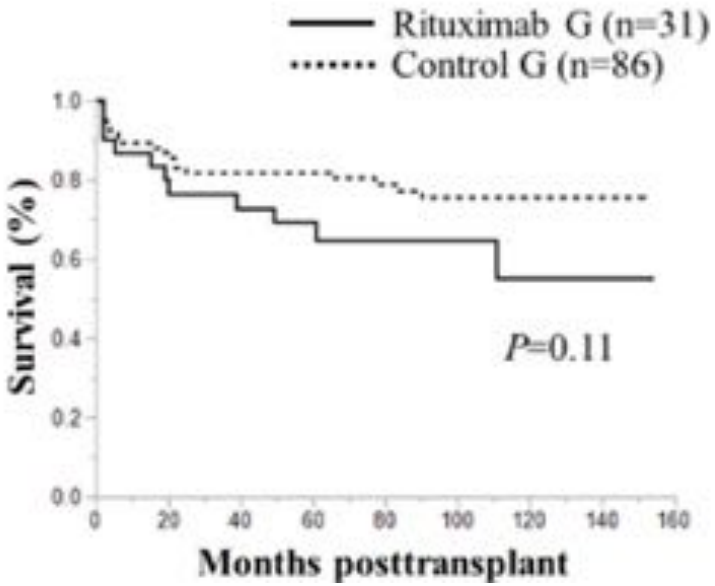


I Fluery et al. Ann Oncol 2016

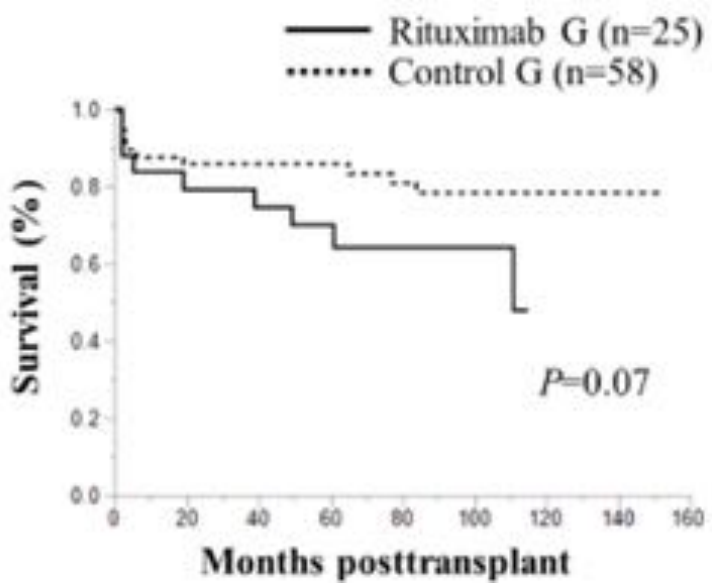
Rituximab and HCC after LDLT

- **Retrospective study of 117 consecutive HCC patients with LDLT (Kyoto University, 2006-2018)**
  - **RTX group (n=31, 30 ABOi + 3 DSA strongly positive (2 also in ABO-I group))**
  - **Control group (n=86)**

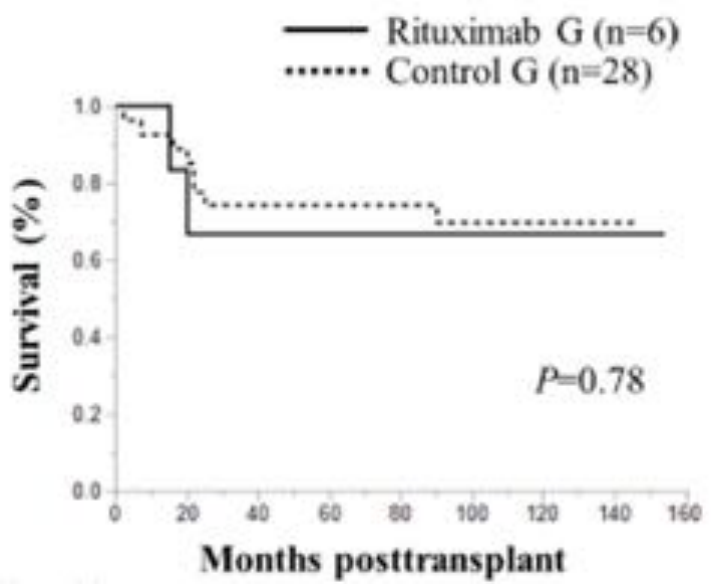
Overall



Within MC



Beyond MC



N Kamo et al. Hepatoma Res 2021

Meta-analysis

ABOi ALDLT + RTX

9 studies

3,922 patients

ABOi = 671

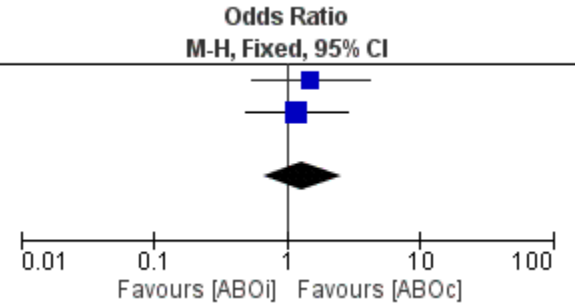
ABOc = 3,251

1 year OS in HCC patients

Study or Subgroup	ABOi Events	ABOi Total	ABOc Events	ABOc Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kim JM (2018)	54	59	159	181	41.3%	1.49 [0.54, 4.14]
Yoon (2018)	159	165	721	753	58.7%	1.18 [0.48, 2.86]
Total (95% CI)		**224**		**934**	**100.0%**	**1.31 [0.67, 2.56]**
Total events	213		880			

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

Test for overall effect: Z = 0.78 (P = 0.43)

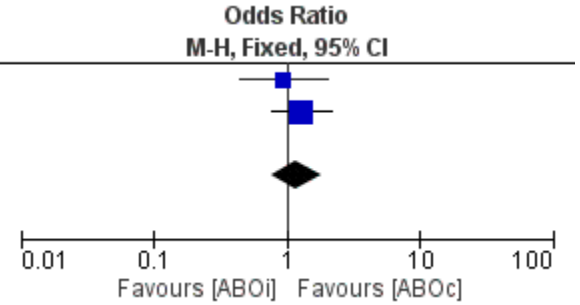


3 year OS in HCC patients

Study or Subgroup	ABOi Events	ABOi Total	ABOc Events	ABOc Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kim JM (2018)	48	59	149	181	34.9%	0.94 [0.44, 2.00]
Yoon (2018)	147	165	650	753	65.1%	1.29 [0.76, 2.20]
Total (95% CI)		**224**		**934**	**100.0%**	**1.17 [0.76, 1.80]**
Total events	195		799			

Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%

Test for overall effect: Z = 0.71 (P = 0.48)

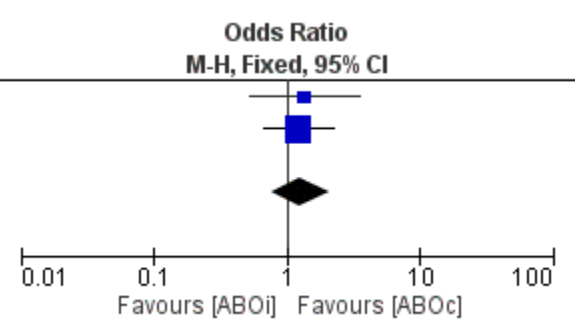


1 year RFS in HCC patients

Study or Subgroup	ABOi Events	ABOi Total	ABOc Events	ABOc Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kim JM (2018)	53	59	157	181	27.6%	1.35 [0.52, 3.48]
Yoon (2018)	151	165	676	753	72.4%	1.23 [0.68, 2.23]
Total (95% CI)		**224**		**934**	**100.0%**	**1.26 [0.76, 2.09]**
Total events	204		833			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%

Test for overall effect: Z = 0.90 (P = 0.37)

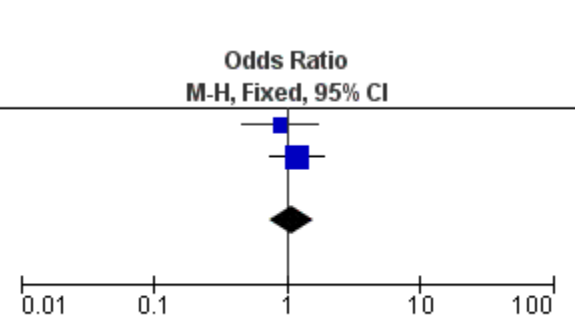


3 year RFS in HCC patients

Study or Subgroup	ABOi Events	ABOi Total	ABOc Events	ABOc Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kim JM (2018)	43	59	136	181	35.6%	0.89 [0.46, 1.73]
Yoon (2018)	141	165	626	753	64.4%	1.19 [0.74, 1.91]
Total (95% CI)		**224**		**934**	**100.0%**	**1.08 [0.74, 1.59]**
Total events	184		762			

Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%

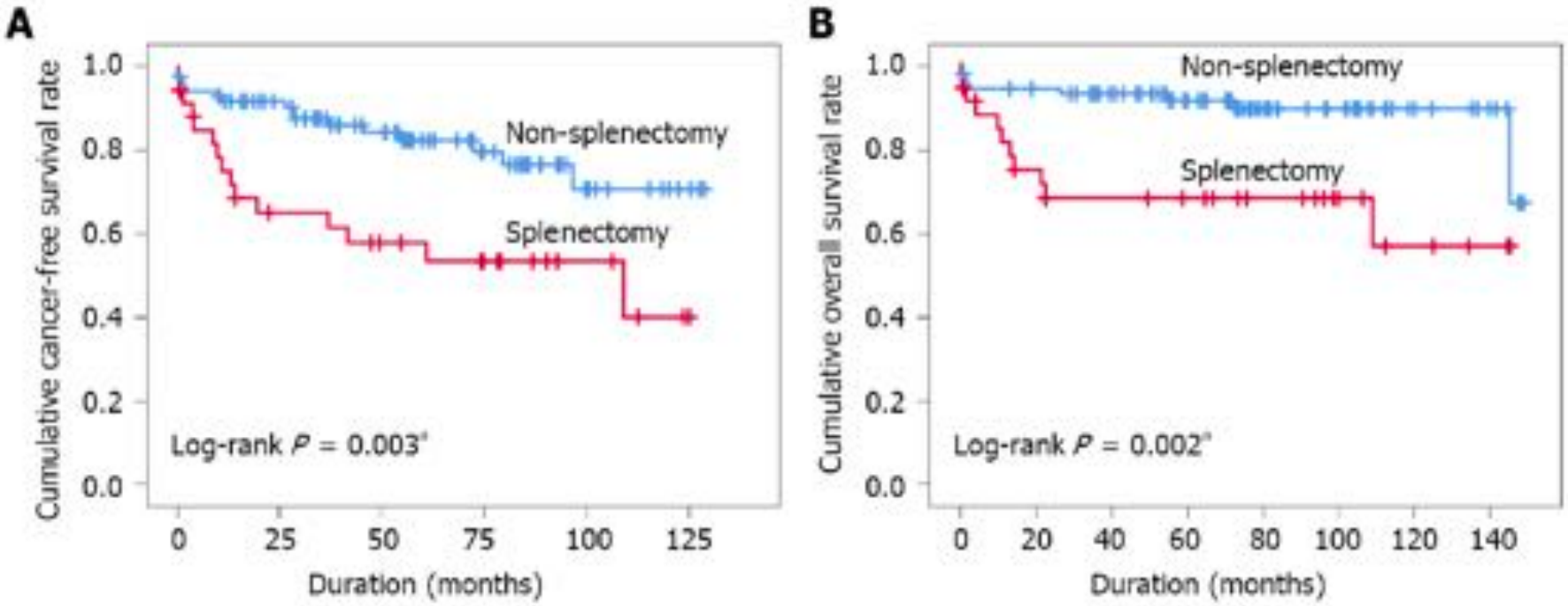
Test for overall effect: Z = 0.41 (P = 0.68)



DK Yadav et al. Gastroenterol Res Prac 2019

Splenectomy Associated with Higher Rates of HCC Recurrence after LT

Retrospective Study of 120 HCC patients within UCSF who received LT with (n = 35) and without (n = 85) simultaneous splenectomy



Splenectomy had higher HCC recurrence (42.9% vs 18.8%, P = 0.011) and mortality (31.4% vs 10.6%, P = 0.013) compared with nonsplenectomy

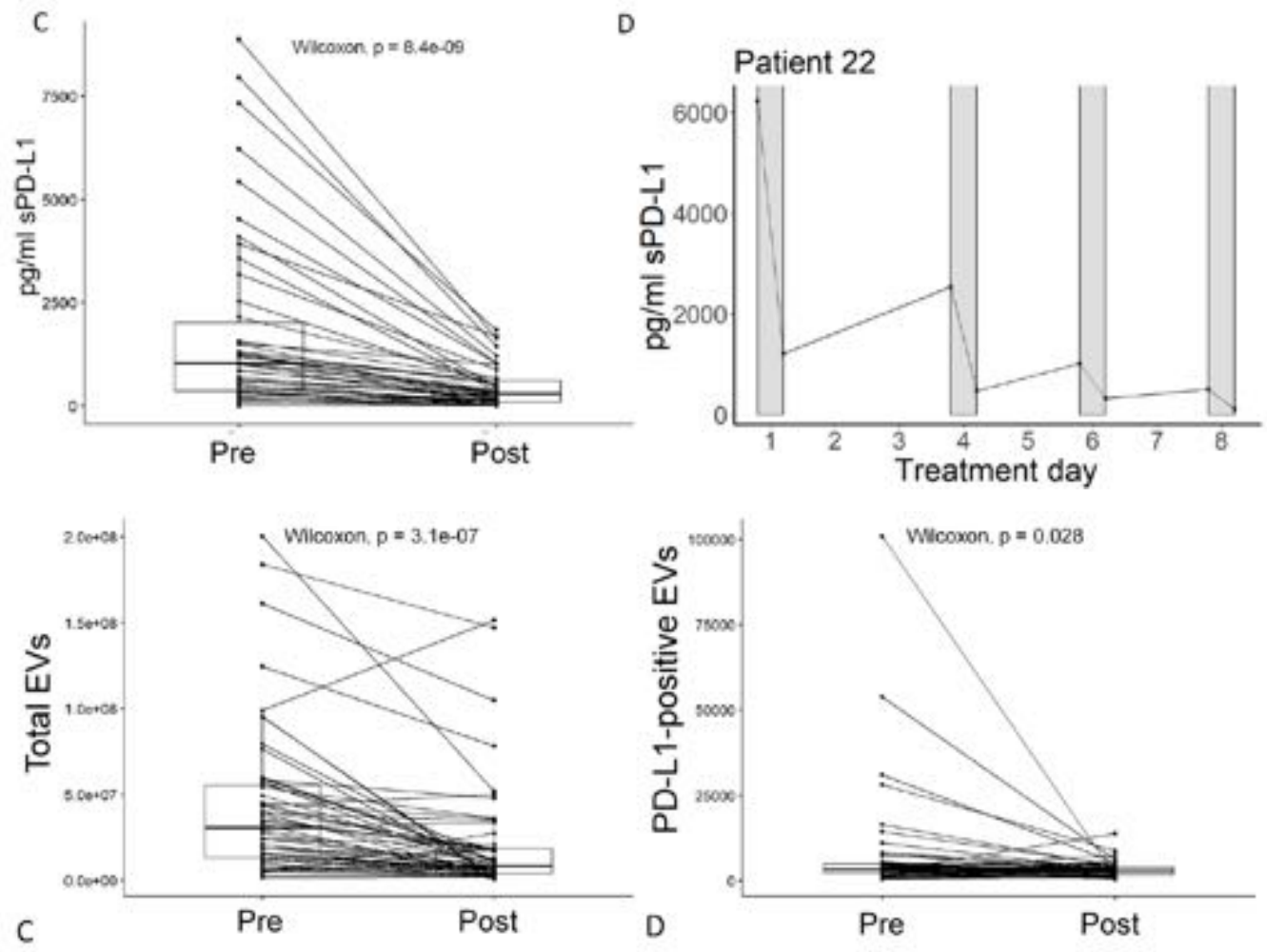
Splenectomy was a positive independent factors for prediction of cancer development [(HR): 2.560, P < 0.05].

Therapeutic Plasma Exchange Reduces Plasma Soluble PD-L1 and PD-L1+ Extracellular Vesicles

- 24 patients undergoing TPE
- Albumin-only (no FFP) replacement fluid

Table 2 Soluble programmed death-ligand 1 (sPD-L1) reduction and regeneration per exchange

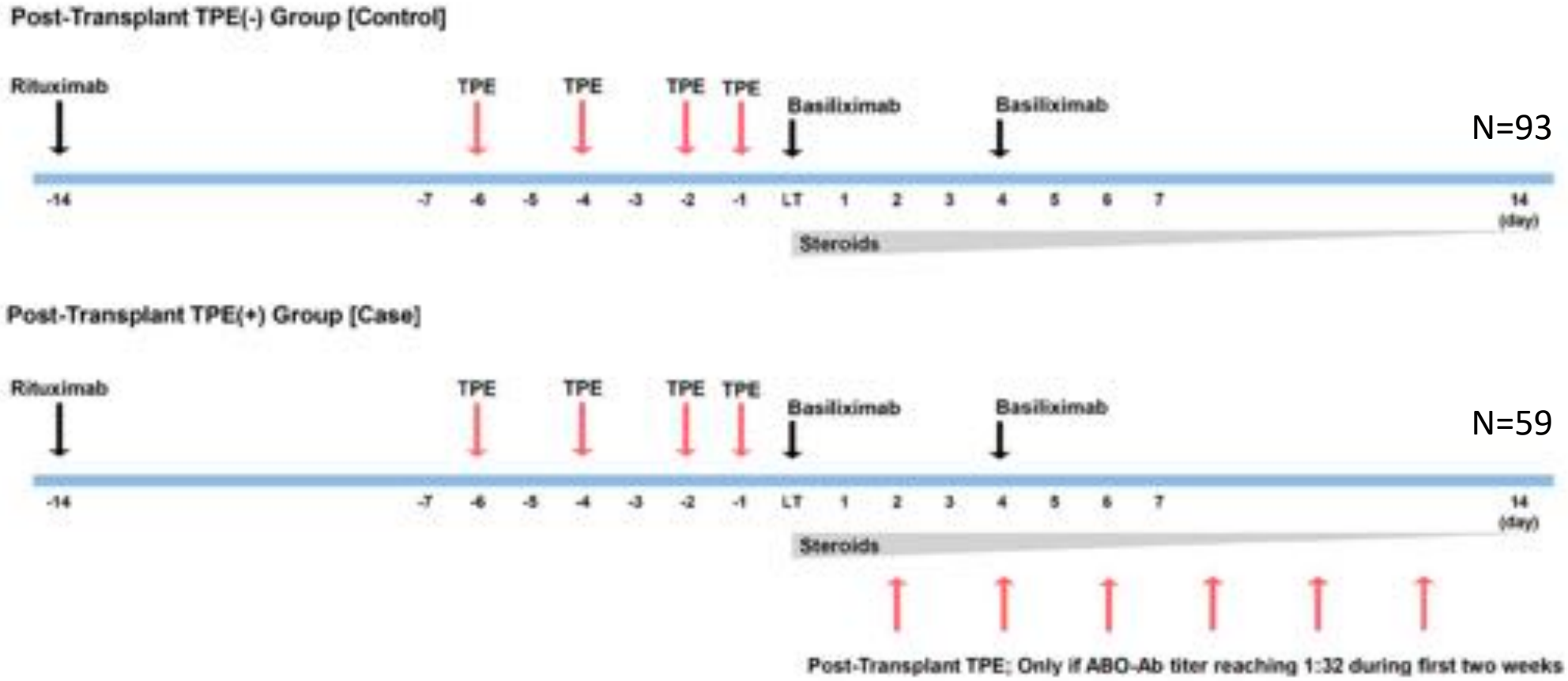
% Reduction per exchange	(n=44)
Mean (SD)	70.8 (21.3)
Median (min, max)	74.4 (−5.10, 100)
% Regeneration between exchanges	**(n=44)**
Mean (SD)	33.8 (84.1)
Median (min, max)	45.5 (−429, 100)
Regeneration per cycle (pg/mL)	
Mean (SD)	1250 (3300)
Median (min, max)	466 (−3.8k, 15.4k)



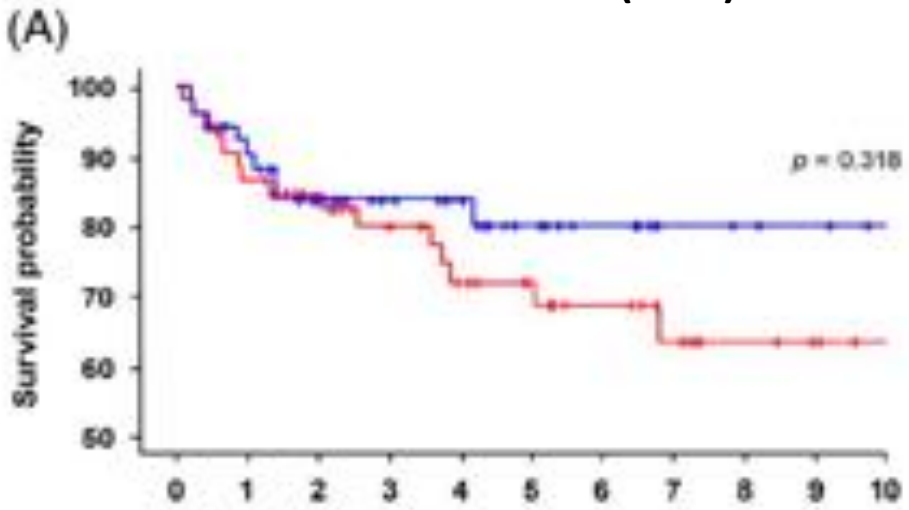
Effect of Total Plasma Exchange on HCC

152 ABOi-LDLT for HCC (Samsung Medical Center, 2010-2021)

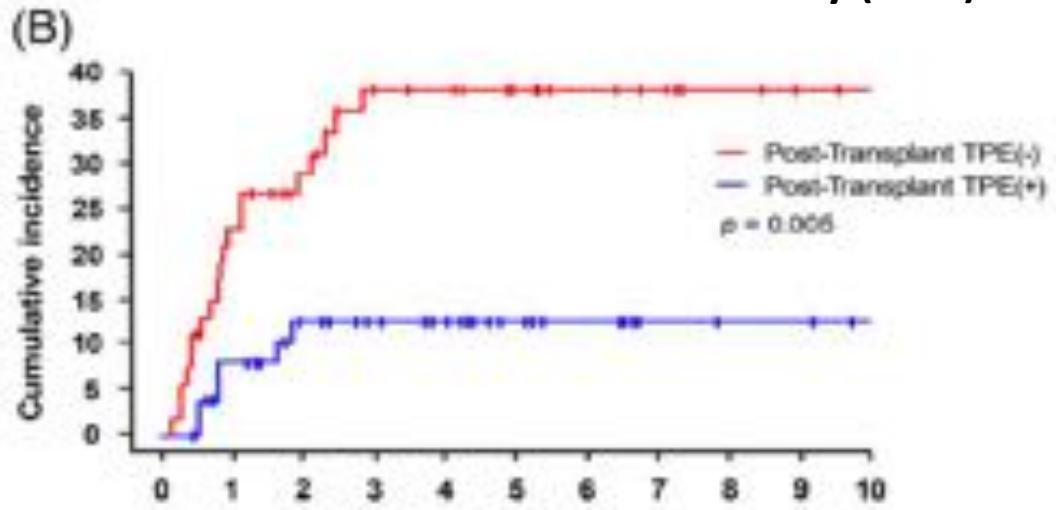
Divided into 2 groups according to whether or not TPE was, in addition, performed postoperatively



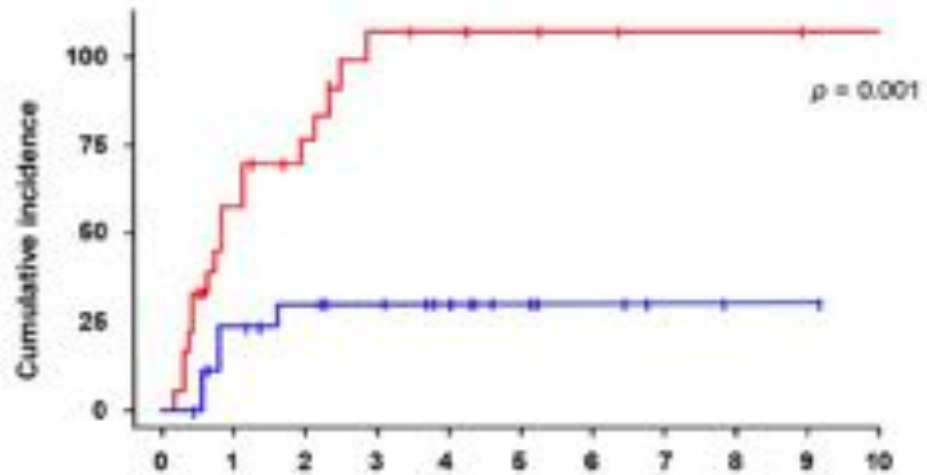
Overall Survival (PSM)



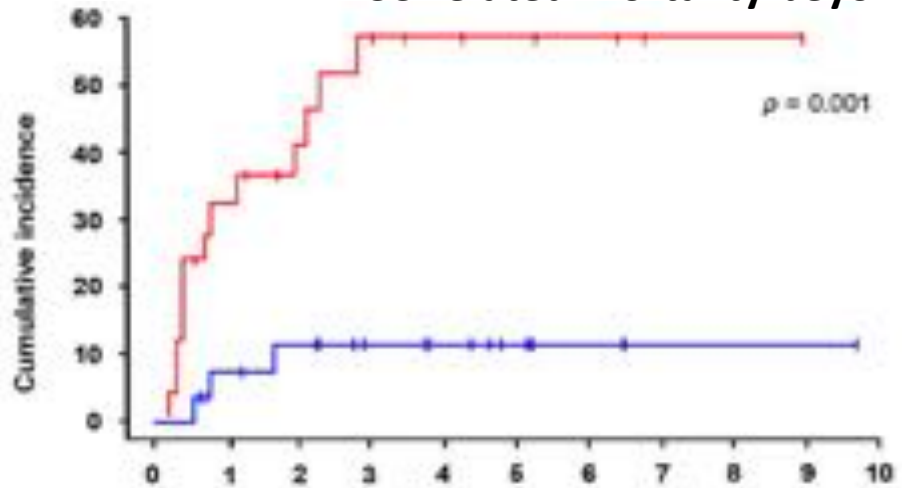
HCC-related mortality (PSM)



HCC-related mortality with MVI



HCC-related mortality beyond MC



Postoperative TPE improved HCC-specific RFS after ABOi LT for HCC, especially in advanced cases such as those with MVI and beyond Milan criteria

N Oh et al. Liver Transpl 2023

Summary

- Evidence for increased HCC recurrence after ABO-I LT has not been consistent, and is limited by a few retrospective single center study
  - Probably increase risk with HCC beyond Milan/advanced HCC
- Most common ABO-I protocol currently is a combination of pre-LT rituximab and plasma exchanges, neither of which appears to increase the risk of malignancies
- For high risk HCCs, consideration should be given to minimizing IS
  - Use of mTOR inhibitor

Thank You Very Much For Your Attention

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