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JUNIO 3-7, 2023

En esta presentación puede haber mención a datos científicos que no están aprobados en el registro. Por favor, consulte la ficha técnica. Las opiniones expresadas en esta presentación corresponden únicamente a quienes las emiten y no representan necesariamente las opiniones de Chiesi España S.A.U.

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AMERICAN TRANSPLANT CONGRESS

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What´s hot, what´s new in Liver Transplant

Laura Benítez

Unidad de Trasplante Hepatico. HU Puerta de Hierro Majadahonda

Impact of OCS Liver Perfusion Time on Post-Transplant Survival - Real World Clinical Experience from the OCS Liver Perfusion (OLP) Post-Approval US Registry

J. F. Markmann[1], M. Hobeika[2], R. Ghobrial[2], G. Roll[3], S. Syed[4], G. Schnickel[5], D. Sudan[6], A. K. Mathur[7], A. Moss[7], M. Abouljoud[8], OLP-Registry-Consortium[9], *[1]Mass General, Boston, MA, [2]Houston Methodist Hospital, Houston, TX, [3]UCSF Medical Center, San Francisco, CA, [4]University of California, San Francisco, San Francisco, CA, [5]University of California Los Angeles (Multi-Organ), San Diego, CA, [6]Duke University Medical Center, Durham, NC, [7]Mayo Clinic, Phoenix, AZ, [8]Henry Ford Transplant Institute, Detroit, MI, [9]Transmedics, Andover, MA*

Background & Methods

- OLP Registry is a multi-center, observational registry collecting OCS ex-vivo perfusion & assessment parameters, as well as short and long-term post-transplant clinical outcomes of liver transplant recipients in the U.S.
- We evaluated the impact of OCS Liver perfusion time on post-transplant survival in the OLP Registry patient cohort to discern any clinical correlation.
- From Oct 2021 – end Mar 2023, 799 livers were transplanted on OCS at 31 centers; data was available for analysis on 763 OCS liver cases
- 3 clinically relevant time points were analyzed:
  - Group A: ≤8 hours of OCS Liver perfusion (N=359)
  - Group B: 8-12 hours of OCS Liver perfusion (N=248)
  - Group C: >12 hours of OCS Liver perfusion (N=156)

Donor Characteristics

	Group A: <= 8hrs (N = 359)	Group B: 8-12hrs (N = 248)	Group C: > 12hrs (N =156)
Gender – n/N (%) Female Male	137/359 (38.16%) 222/359 (61.84%)	95/248 (38.31%) 153/248 (61.69%)	56/156 (35.9%) 100/156 (64.10%)
Age (years) – mean (range)	43.4 (14 – 83)	43.6 (8 – 78)	42.9 (14 – 78)
Donor Type – n/N (%) DBD DCD	201/359 (55.99%) 158/359 (44.01%)	135/248 (55.44%) 113/248 (45.56%)	58/156 (37.18%) 98/156 (62.82%)
DCD WIT (mins) – mean (range)	24.1 (10 – 106)	24.3 (8 – 74)	24.5 (13 – 93)
History of diabetes	53/359 (14.76%)	32/248 (12.90 %)	18/156 (11.54%)
History of drug use	181/359 (50.42%)	135/248 (54.44%)	71/156 (45.51%)
History of excess alcohol use	83/359 (23.12%)	59/248 (23.79%)	28/156 (17.95%)
Macrosteatosis >=40%	7/359 (1.95%)	9/248 (3.63%)	5/156 (3.21%)

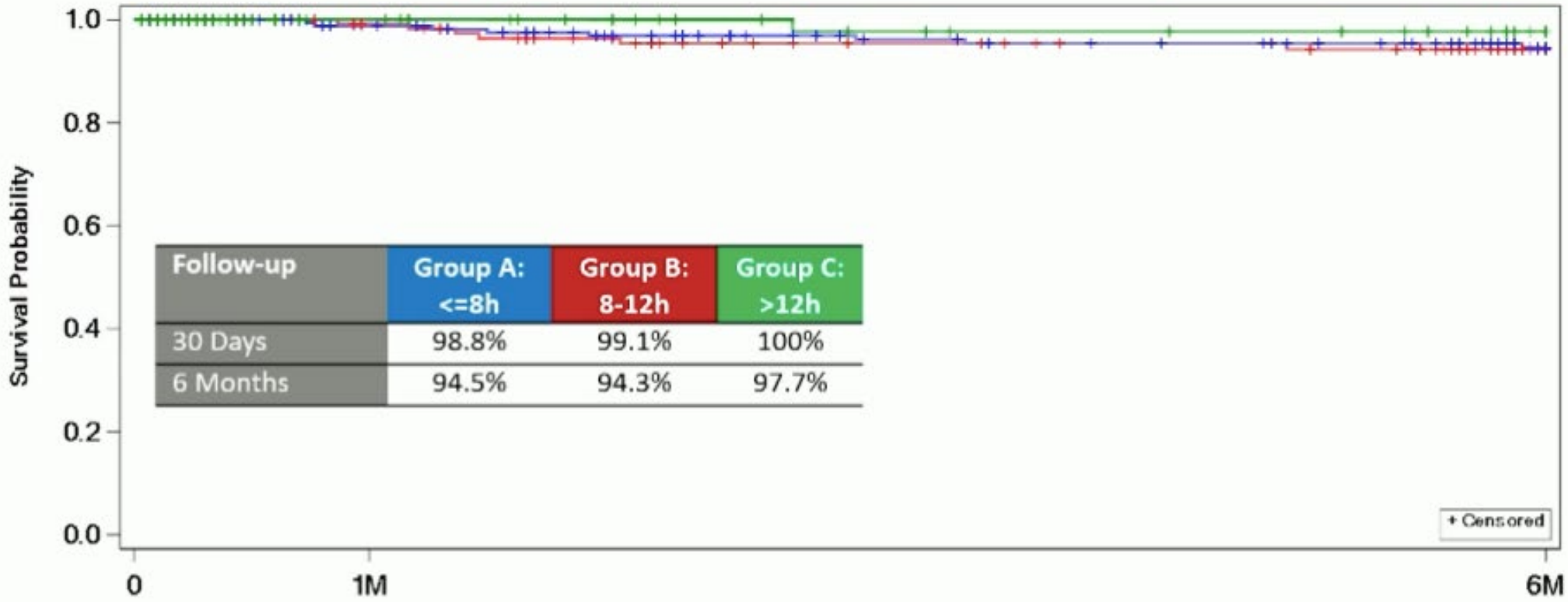
Recipient Characteristics

	Group A: <= 8hrs (N = 359)	Group B: 8-12hrs (N = 248)	Group C: > 12hrs (N =156)
Gender – n/N (%) Female Male	142/359 (39.55%) 217/259 (60.45%)	76/248 (30.65%) 172/248 (69.35%)	48/156 (30.77%) 108/156 (69.23%)
Age (years) – mean (range)	55.9 (0 – 77)	56.5 (24 – 75)	56.1 (18 – 75)
MELD – mean (range)	23.6 (6 – 43)	23.1 (6 – 40)	20.4 (6 – 40)
Previous Any Organ Transplant (%)	21/359 (5.85%)	12/248 (4.84%)	5/156 (3.21%)
Previous Liver Transplant (%)	18/359 (5.01%)	10/248 (4.03%)	5/156 (3.21%)
Multiple Organ Transplant (%)	49/359 (13.65%)	35/248 (14.11%)	14/156 (8.97%)

Impact of OCS Liver Perfusion Time on Post-Transplant Survival- Real World Clinical Experience from OCS Liver Perfusion (OLP) Post-Approval US Registry

	Group A: <= 8hrs (N = 359)	Group B: 8-12hrs (N = 248)	Group C: > 12hrs (N =156)
Donor to Recipient Hospital Distance (miles)	6.53 (0.39 – 17.86)	6.28 (0.30 – 16.55)	6.65 (0.34 – 14.84)
Recipient Location Home Hospital (floor) ICU	 198/359 (55.15%) 56/359 (15.60%) 45/359 (12.53%)	 149/248 (60.08%) 37/248 (14.92%) 25/248 (10.08%)	 99/156 (63.46%) 14/156 (8.97%) 8/156 (5.13%)
Timing of Recipient Case (Night)	46.94%	19.14%	6.56%
Post-transplant length of stay	14.0 (3 – 114)	12.0 (3 – 154)	11.1 (3 – 63)

Patient Survival by Perfusion Group



Follow-up	Group A: <=8h	Group B: 8-12h	Group C: >12h
30 Days	98.8%	99.1%	100%
6 Months	94.5%	94.3%	97.7%

Conclusions

- OCS Liver system perfusion times were associated with good post-transplant survival even when they extended beyond 12 hours.
- Some trends were evident: 1) OCS> 12h had more DCD's, fewer donor comorbidities, recipients with lower MELD, fewer from ICU, fewer night cases, shorter LOS, lower final lactate, and better survival.
- These findings have two important clinical implications:

  (1) the OCS Liver can be utilized to transport and preserve donor livers from outside the recipients' standard acceptance radius, and

  (2) the OCS Liver can be used to perfuse the donor livers overnight to better manage transplant procedure logistics.

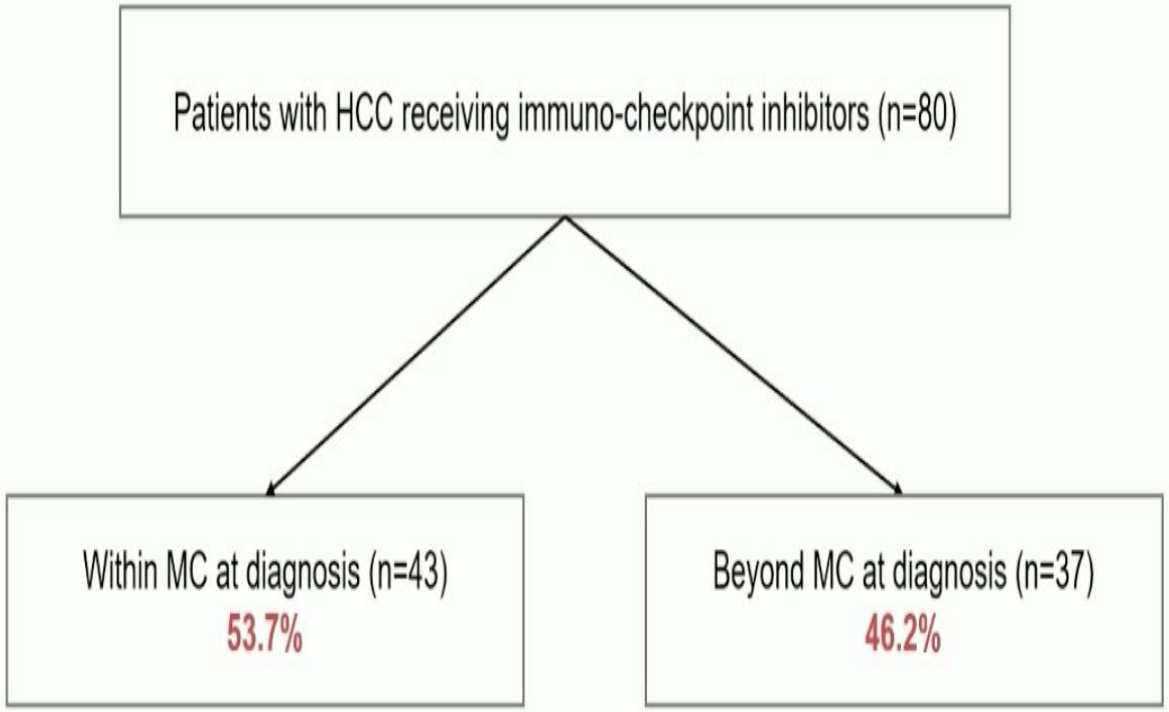
Impact of Immune Checkpoint Inhibitors Pre-Transplantation: Intention to Treat Outcomes from a Multi-Center Study

Parissa Tabrizian, Yuki Bekki, Veeral Ajmera, Amy Kim, Kali Zhou,
Gabriel Schnickel, Kelly Torosian, Maarouf Hoteit, Francis Yao,
Sander Florman, Myron Schwartz, Neil Mehta

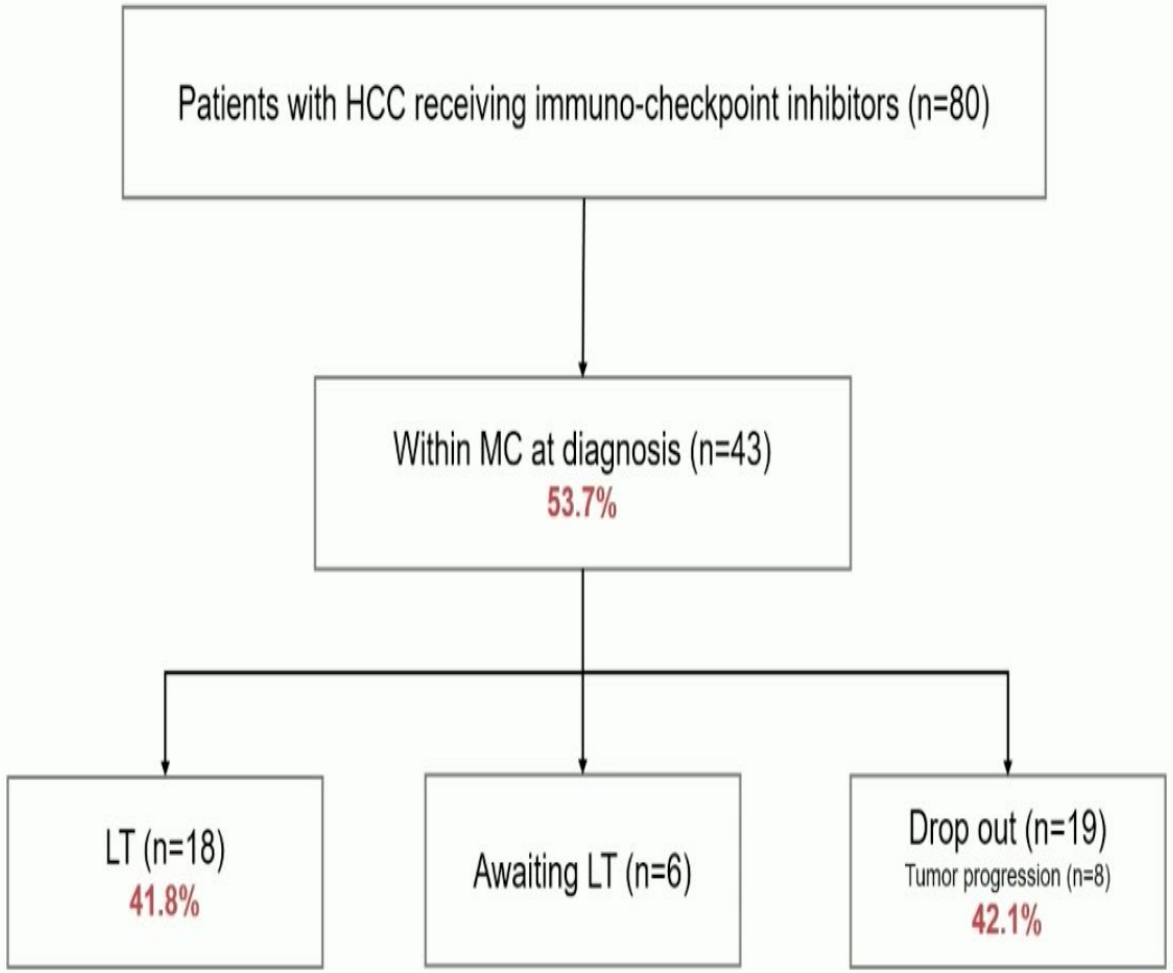
Impact of Inmune Checkpoint Inhibitors Pre-Transplantation: Intention to treat Outcomes from a Multi-Center Study

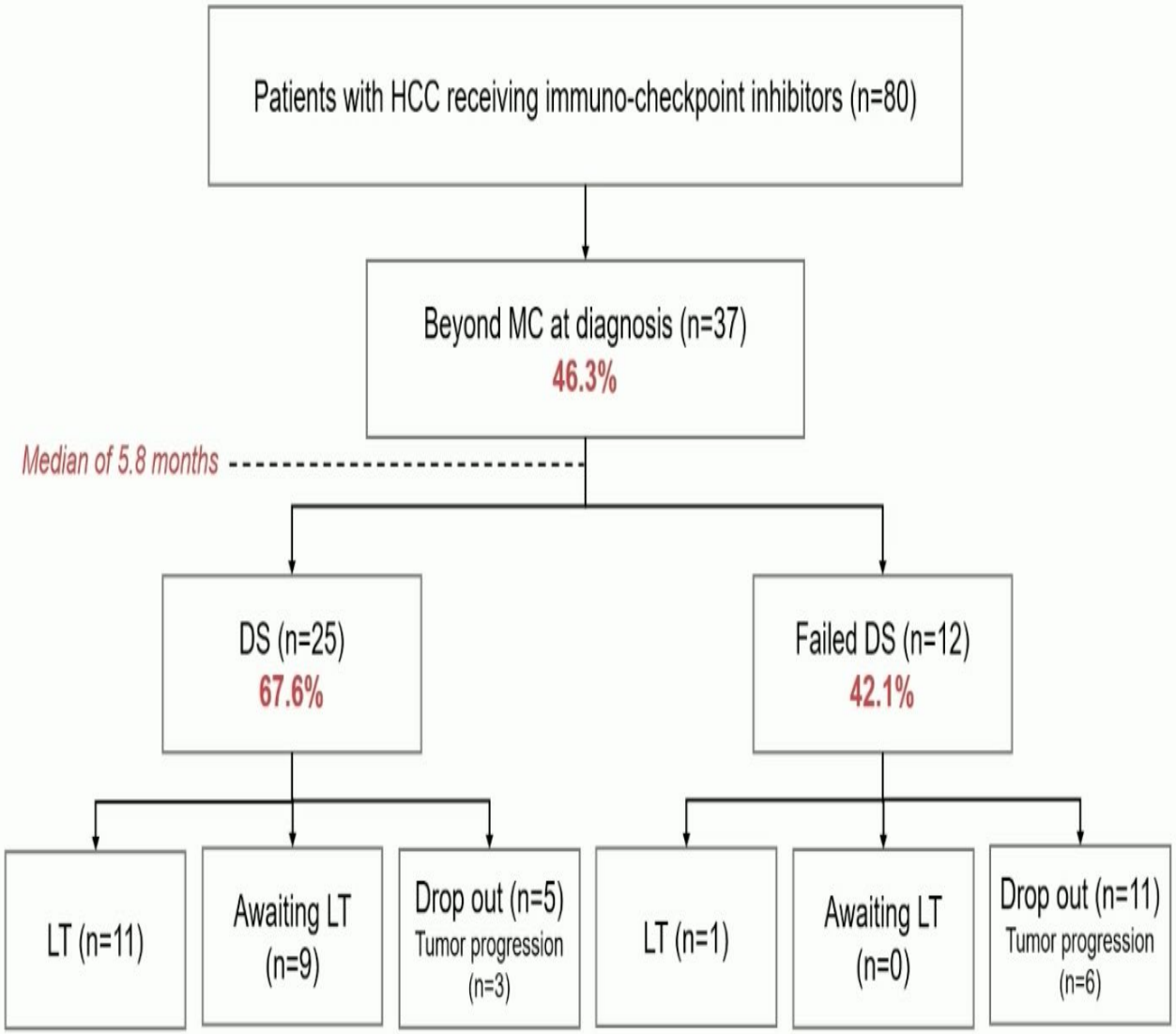
Aim

- Safety of ICI as bridge to LT
- Overall survival and recurrence (ITT and post-LT)
- Predictors of dropout from the waiting list
- Predictors of rejection post LT



Impact of Inmune Checkpoint Inhibitors Pre-Transplantation: Intention to treat Outcomes from a Multi-Center Study





The 3-year cumulative probability of dropout was 44.8% if within MC

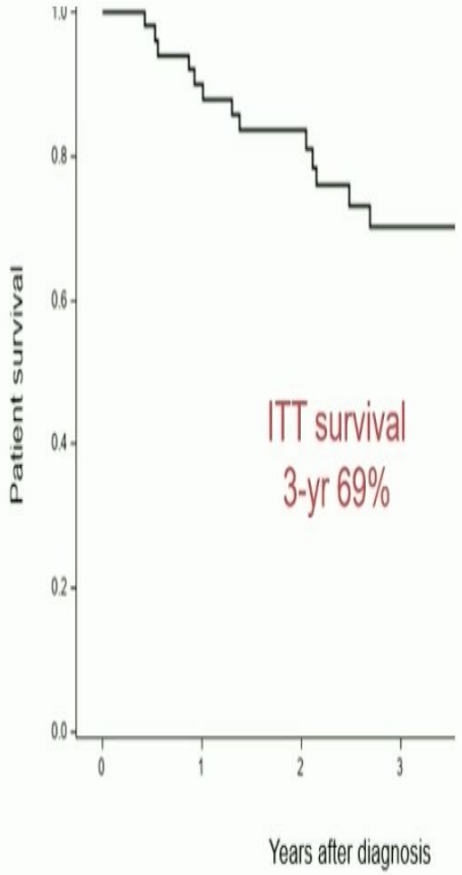
The 3-year cumulative probability of dropout 53.7% beyond MC

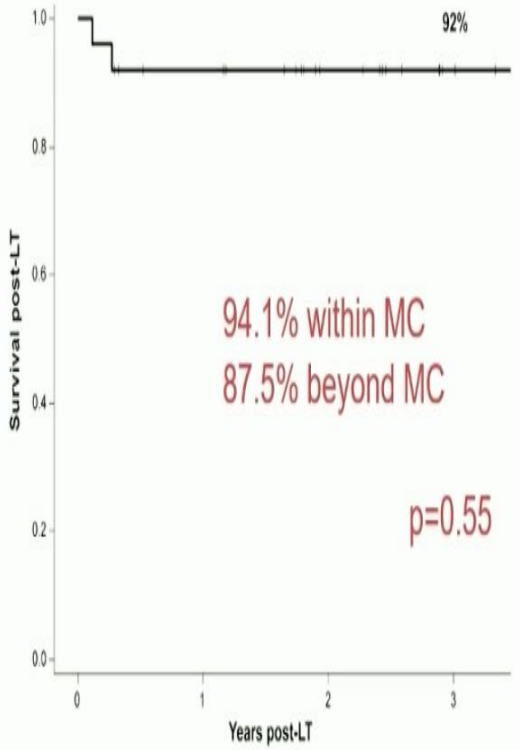
Impact of Inmune Checkpoint Inhibitors Pre-Transplantation: Intention to treat Outcomes from a Multi-Center Study

Rejection post LT

- Post-LT rejection rate was 16.6%
  - n=2 severe, 1 graft loss and re-LT
  - n=3 mild secondary to low immunosuppression
- ICI dose < 3 months pre-LT was associated with increased rejection (p=0.04)

Overall survival (ITT and post LT)





Conclusions

- First multi-center ITT study on ICI in pre LT setting
- 67% DS to within MC at a median of 5.8 months
- No grade 4-5 adverse events were reported on the wait list
- Post-LT rejection rate was 16.6% -→ predictor: ICI dose < 3 months pre LT

→ Minimal washout/observation period 3 months pre LT

- Encouraging pathologic response
- ITT survival at 3 years from diagnosis nearly 70%
- Clinical trials

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Session 15 - Liver: Immunosuppression and Rejection

22 - Distinguishing an Antibody-Mediated Rejection-Like State in Liver Transplants with High Expression of NK Cell Transcripts and IFNG-Induced Transcripts

June 3, 2023, 4:15 PM - 4:25 PM | Ballroom 6C Upper Level

Authors

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Distinguishing an Antibody-Mediated Rejection-Like State in Liver Transplants with High Expression of NK Cell Transcripts and IFNG_Induced Transcripts

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Background

Initial molecular analysis of liver biopsies using rejection-associated transcripts (AJT 20: 2156 2020) failed to find a DSA+ve ABMR phenotype similar to kidney transplants.

Recent kidney studies (AJT 22:1976, 2022) show that ABMR is **often DSA-ve but consistently has NK cell transcripts**.

We investigated whether a ABMR-like state exists in liver transplants, potentially missed because it is DSA-ve.

Methods

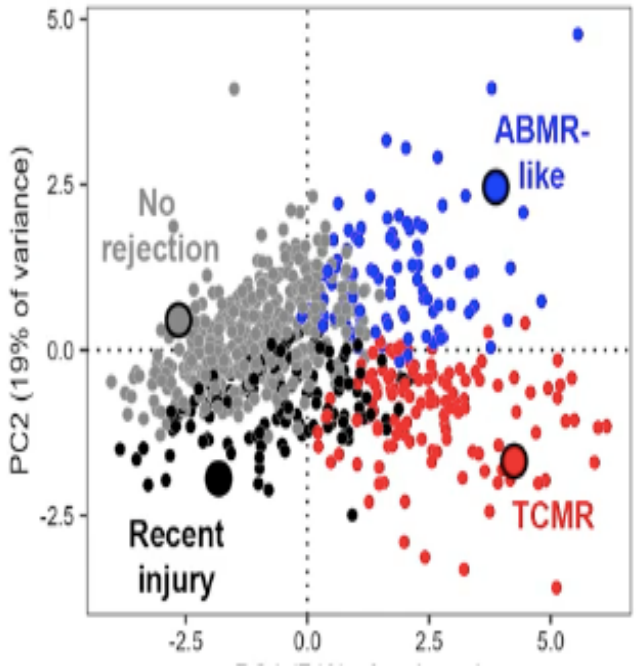
Samples assessed using genome-wide gene expression (microarrays, the Molecular Microscope® Diagnostic System).

Optimized feature selection maximized separation between TCMR and 'ABMR-like' features (validated in training/test set) and generated

Results

4 archetype groups assigned: No-rejection (NR) N=416; TCMR N=125; ABMR-like N=98; and **Recent Injury/no rejection** (RI) N=126.

A.



Distinguishing an Antibody-Mediated Rejection-Like State in Liver Transplants with High Expression of NK Cell Transcripts and IFNG_Induced Transcripts

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Results (continued)

ABMR-like score top transcripts **almost exclusively expressed in NK cells.**

DSA status known for 157 biopsies, 76 DSA+ve. **DSA was not increased in ABMR-like cases.**

TCMR scores correlated strongly with T cell burden and abnormal biochemistry. **ABMR-like scores correlated with NK cells but not with DSA or abnormal biochemistry.**

The relatively few reported graft failures mostly followed TCMR, not ABMR-like biopsies.

CONCLUSIONS

1. Some liver transplants develop a clinically-silent, **ABMR-like state of unknown significance (separate from TCMR).**
2. This state characterized by **NK cell and IFNG-inducible transcripts with little parenchymal injury, similar to early-stage ABMR in kidneys but not consistently DSA+ (potential absorption by liver).**
3. These changes in heart & kidney transplants lead to atrophy-fibrosis - **consequences in liver should be studied.**

Rifaximin treatment improves liver transplant outcomes by promoting hepatocellular regeneration

Hidenobu Kojima, Shoichi Kageyama, Daisuke Noguchi,
Kenneth J. Dery, Taylor Torgerson, Kentaro Kadono, Hirofumi Hirao,
Kojiro Nakamura, Siyuan Yao, Fady M. Kaldas, Jerzy W. Kupiec-Weglinski

The Dumont-UCLA Transplantation Center, Department of Surgery,
David Geffen School of Medicine at UCLA

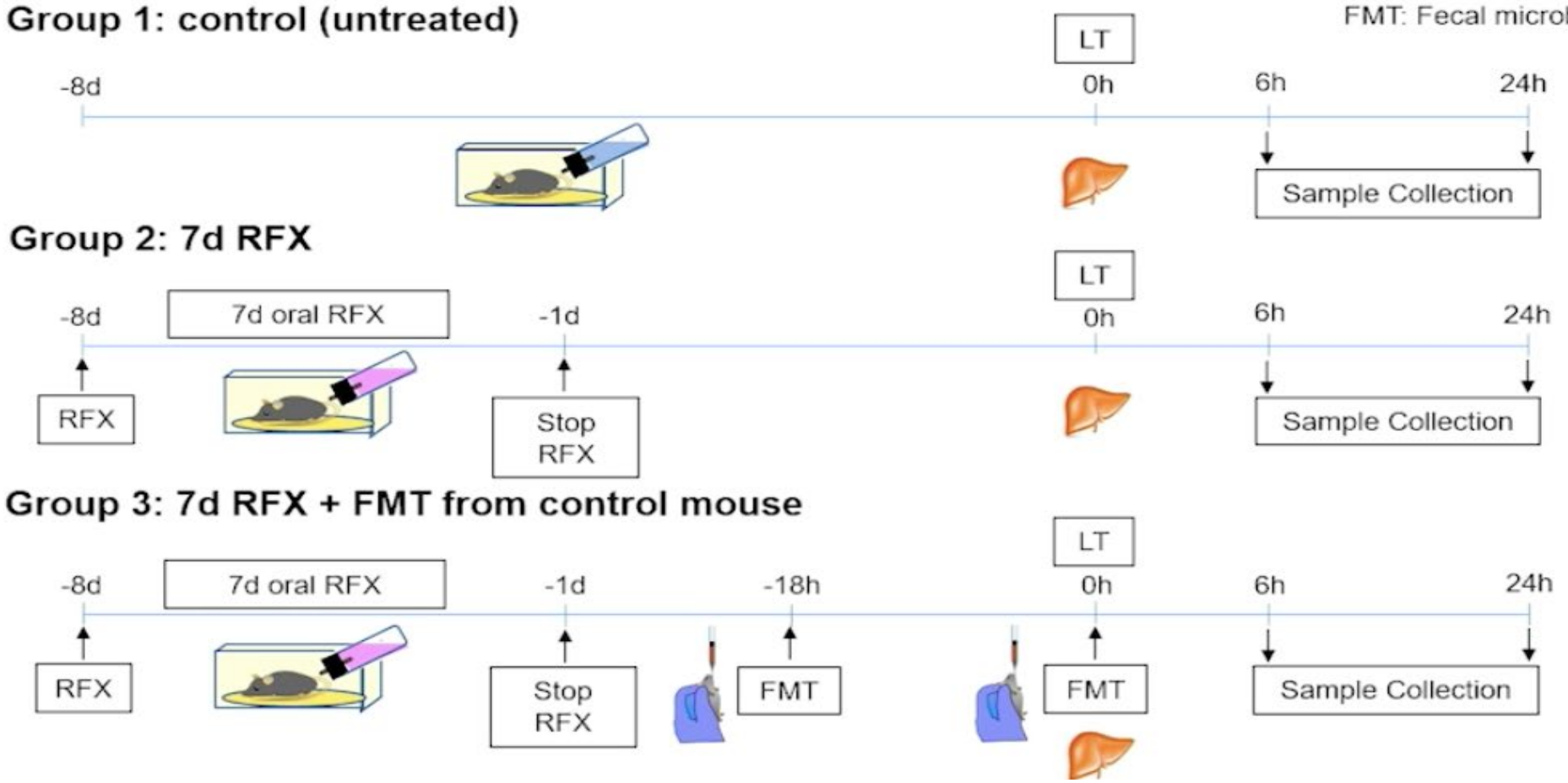
Aim of this study

- To clarify whether and how pre-LT rifaximin treatment affects liver transplant outcomes

Rifaximin treatment improves liver transplant outcomes by promoting hepatocellular regeneration

Methods: animal study

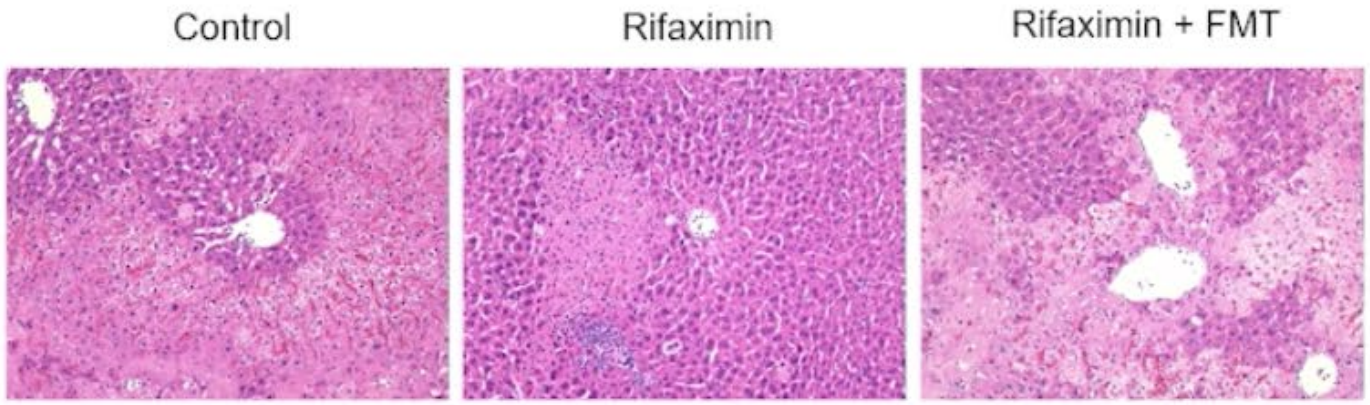
LT: Liver transplantation
RFX: Rifaximin
FMT: Fecal microbiota transplantation

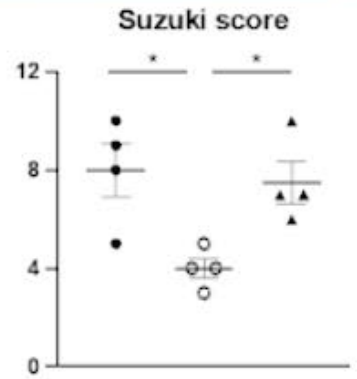


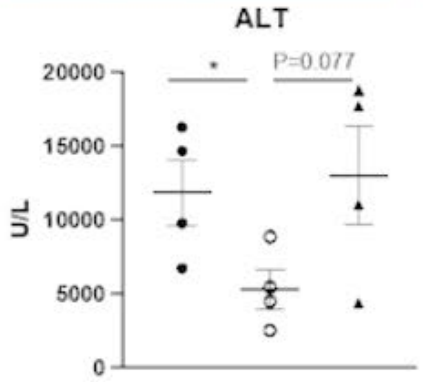
Rifaximin treatment improves liver transplant outcomes by promoting hepatocellular regeneration

Pre-transplant RFX treatment mitigated LT injury and FMT restored the liver injury

C57BL/6 to C3H



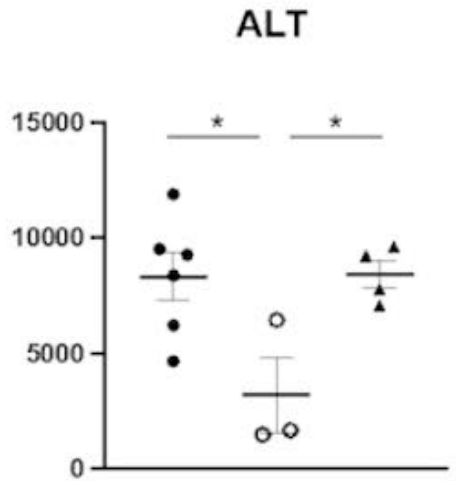




*p<0.05

Control	n=4
Rifaximin	n=4
Rifaximin + FMT	n=4

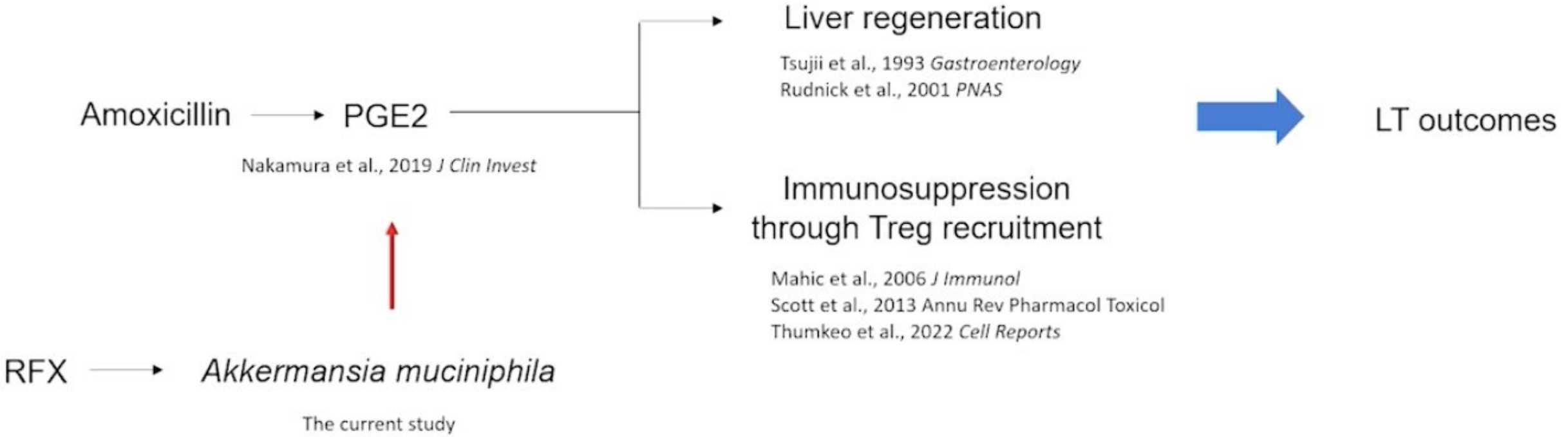
Balb/c to C57BL/6



Control	n=6
Rifaximin	n=3
Rifaximin + FMT	n=4

Rifaximin treatment improves liver transplant outcomes by promoting hepatocellular regeneration

Putative mechanism

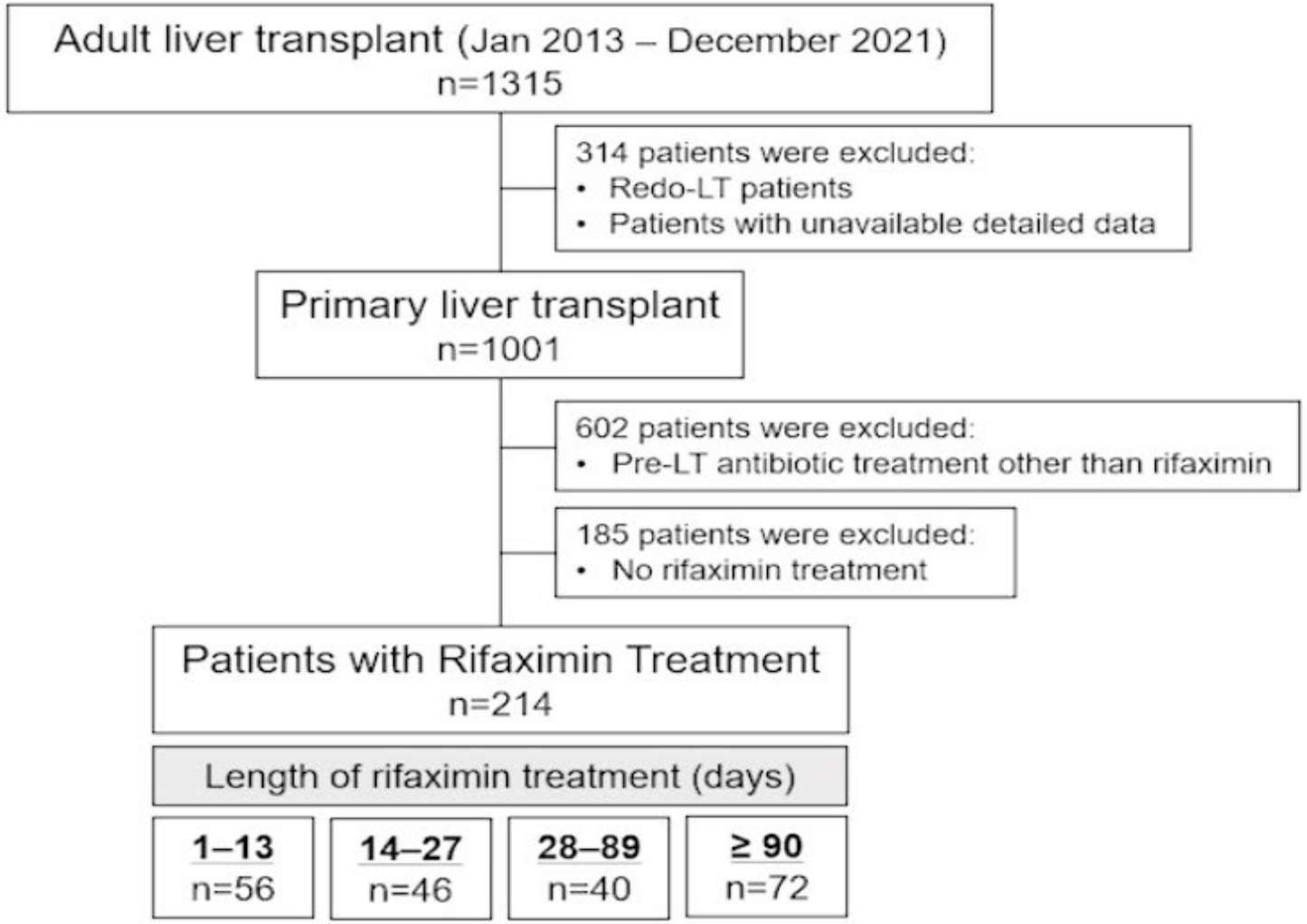


Summary 1

- Pretransplant rifaximin treatment mitigated liver injury and enhanced liver regeneration following LT in mice.
- The effect of rifaximin was counteracted by FMT.
- 16S sequencing identified that *Akkermansia muciniphila* increased in two different mouse species treated by rifaximin.

Rifaximin treatment improves liver transplant outcomes by promoting hepatocellular regeneration

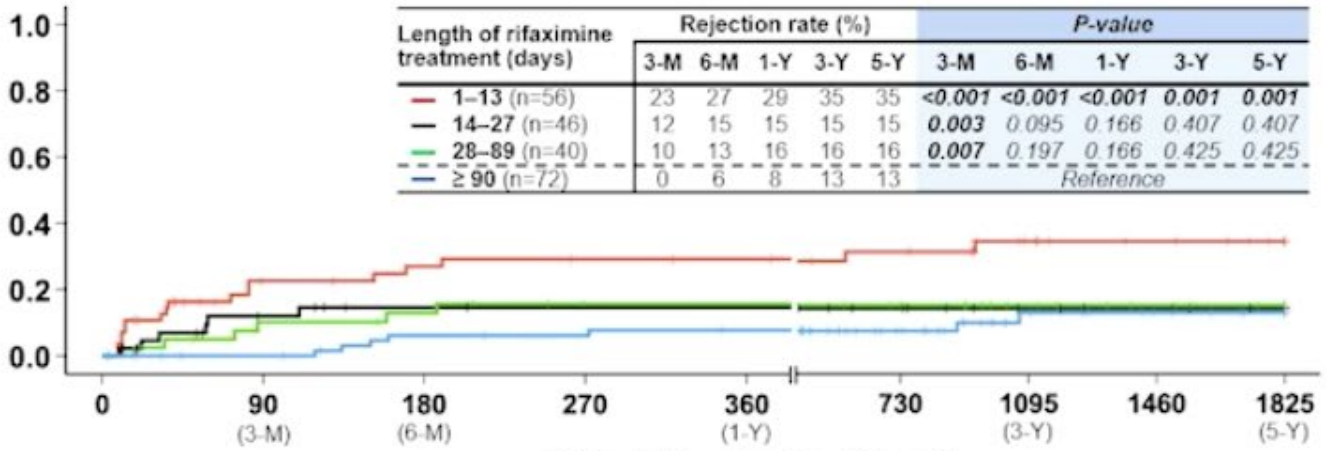
Methods: retrospective study in human patients



Rifaximin treatment improves liver transplant outcomes by promoting hepatocellular regeneration

Longer RFX treatment reduced allograft rejection

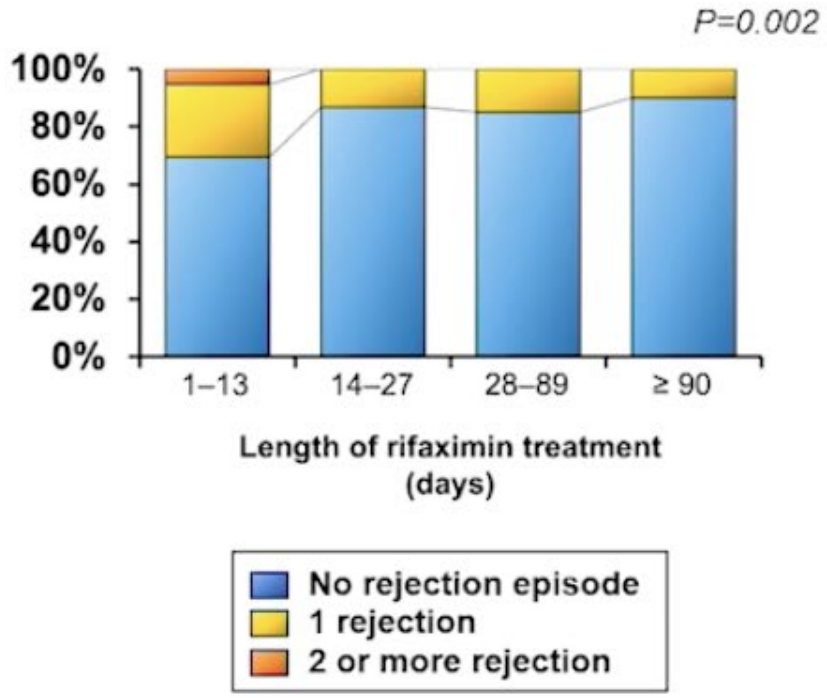
Cumulative rejection rate



Length of rifaximine treatment (days)	Rejection rate (%) 3-M	6-M	1-Y	3-Y	5-Y	*P-value* 3-M	6-M	1-Y	3-Y	5-Y
1–13 (n=56)	23	27	29	35	35	*<0.001*	*<0.001*	*<0.001*	*0.001*	*0.001*
14–27 (n=46)	12	15	15	15	15	*0.003*	*0.095*	*0.166*	*0.407*	*0.407*
28–89 (n=40)	10	13	16	16	16	*0.007*	*0.197*	*0.166*	*0.425*	*0.425*
≥ 90 (n=72)	0	6	8	13	13	*Reference*				

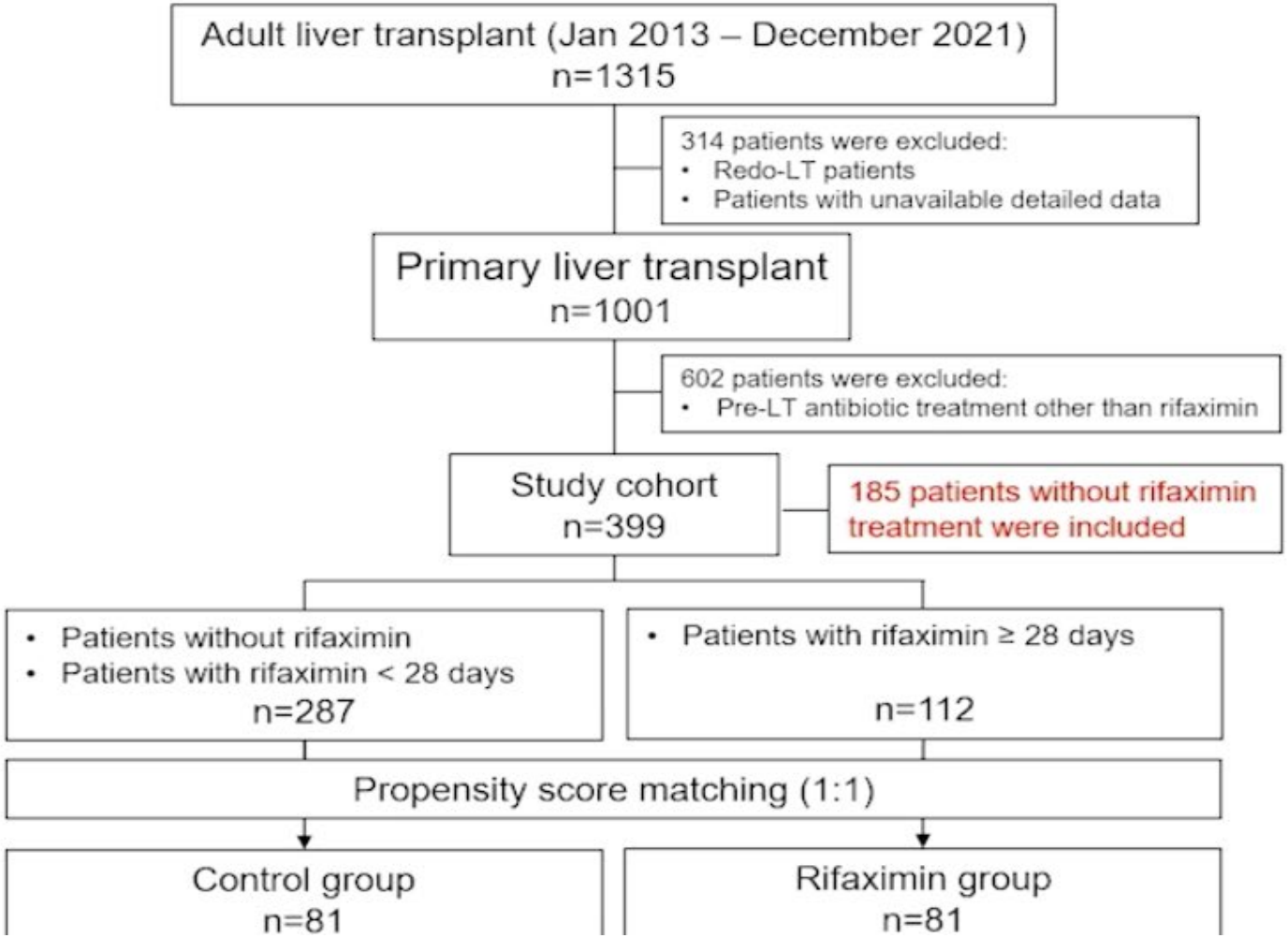
No. at risk									
1–13 days	56	36	33	30	17	24	17	13	9
14–27 days	46	34	30	29	29	24	19	17	14
28–90 days	40	34	32	28	28	25	20	16	13
≥ 90 days	72	67	61	60	58	42	28	23	19

Rejection rate



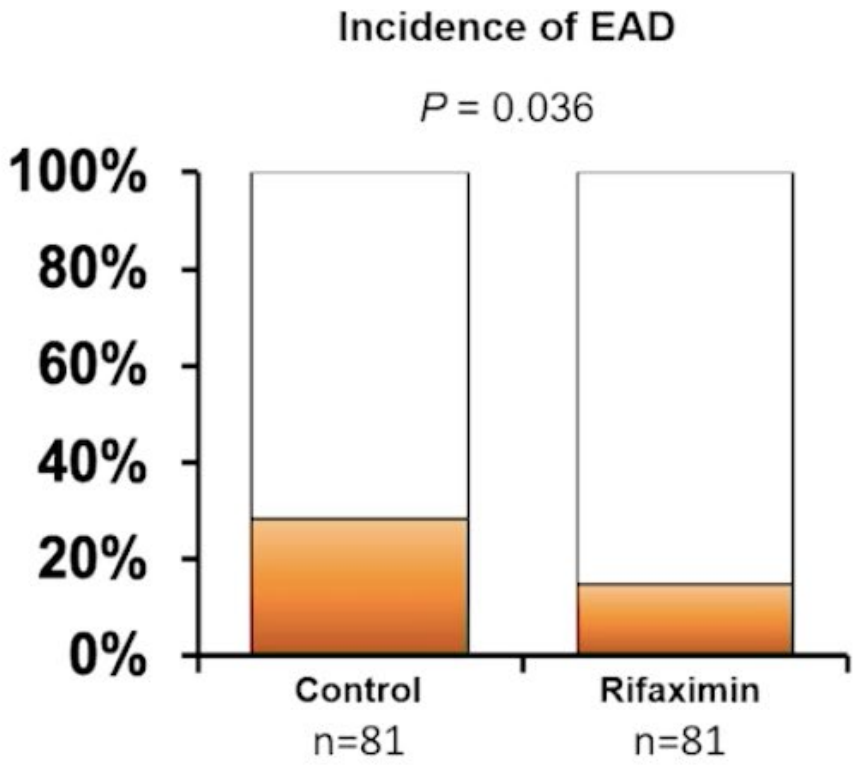
Rifaximin treatment improves liver transplant outcomes by promoting hepatocellular regeneration

Methods: retrospective study in human patients



Rifaximin treatment improves liver transplant outcomes by promoting hepatocellular regeneration

Pre-transplant RFX treatment ≥ 28 days reduced incidence of early graft dysfunction (EAD)



Summary 2

- In the clinical LT, patients with ≥ 28 d pretransplant rifaximin treatment significantly reduced EAD and improved rejection-free survival

Conclusions

- This study demonstrates the effectiveness of RFX therapy prior to LT in mice and humans.
- *Akkermansia muciniphila* mediated by pretransplant RFX therapy could contribute to improving LT outcomes.