Challenges and Opportunities in Development of Therapeutics for MASH After Liver Transplant

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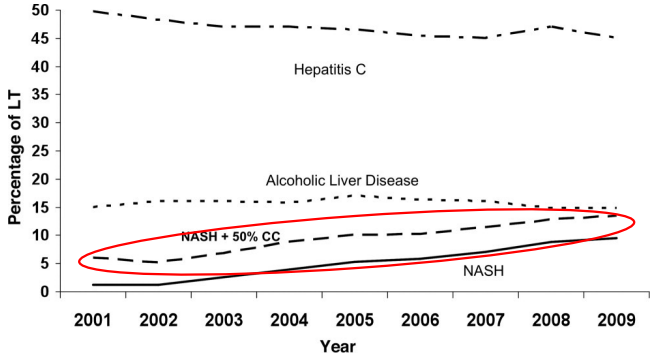
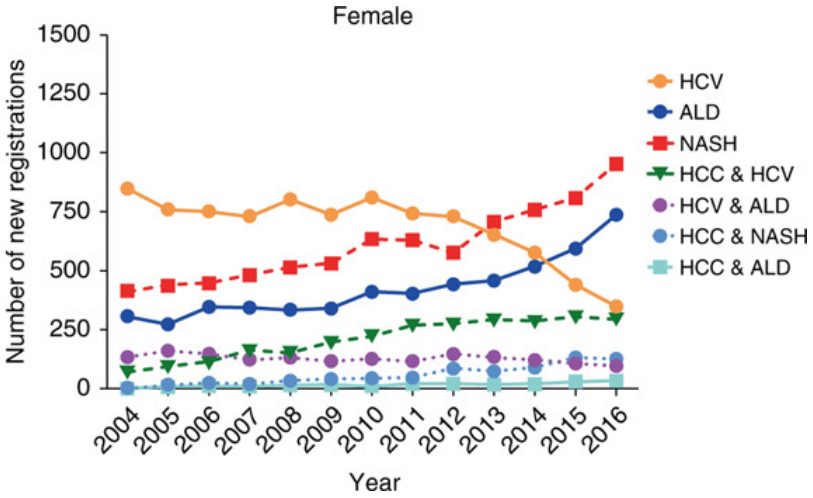
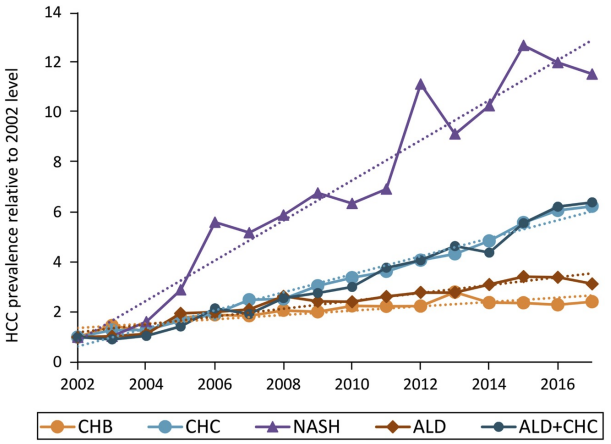
Conflict of Interest Disclosures

- Advisory board: AMRA Medical
- Data Safety Monitoring Board: Sagimet
- NovoNordisk

MASH Cirrhosis is an Important Indication for Liver Transplantation







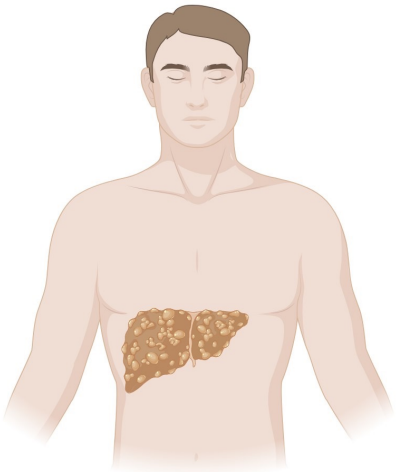
Charlton et al. Gastroenterology. 2012

Noureddin et. al. Am J Gastro 2018

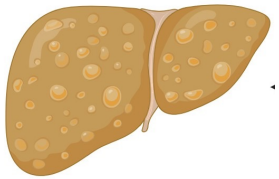
Younossi et. al. CGH 2019

Recurrence Vs. De Novo MASLD Following Transplant

MASH Cirrhosis



POST LT MASLD



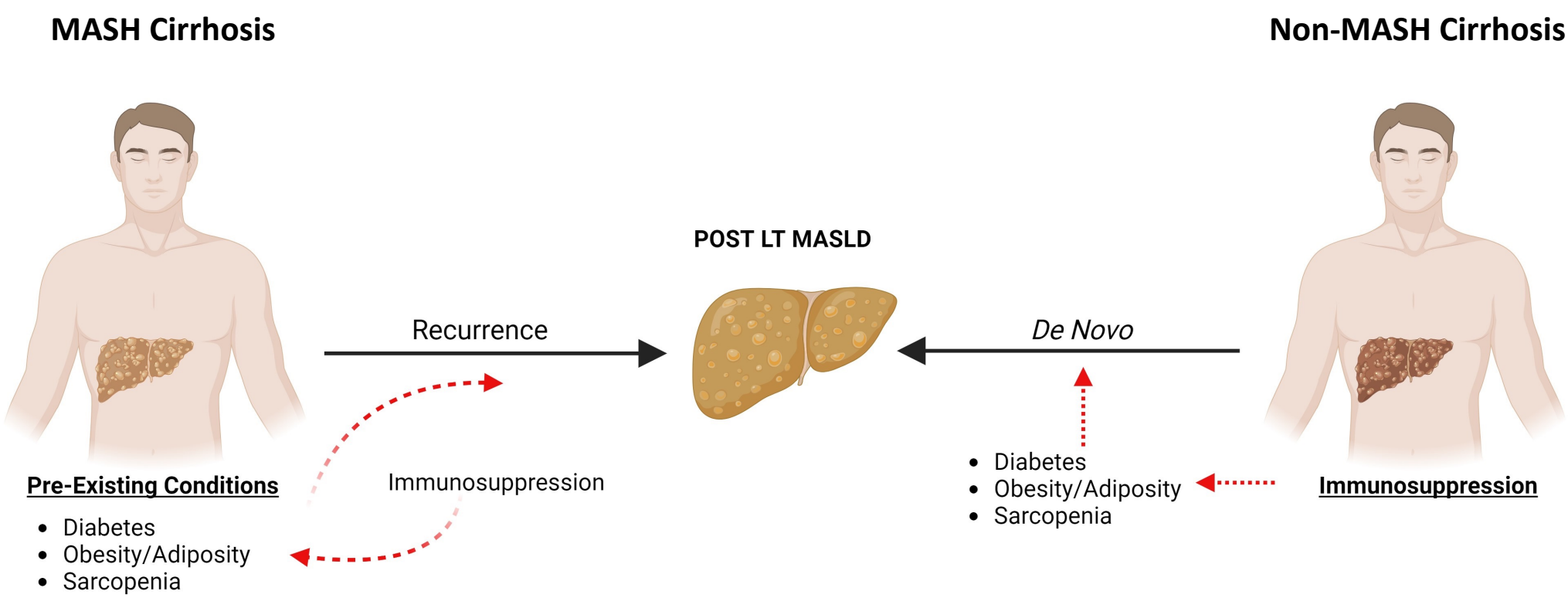
Recurrence

Immunosuppression

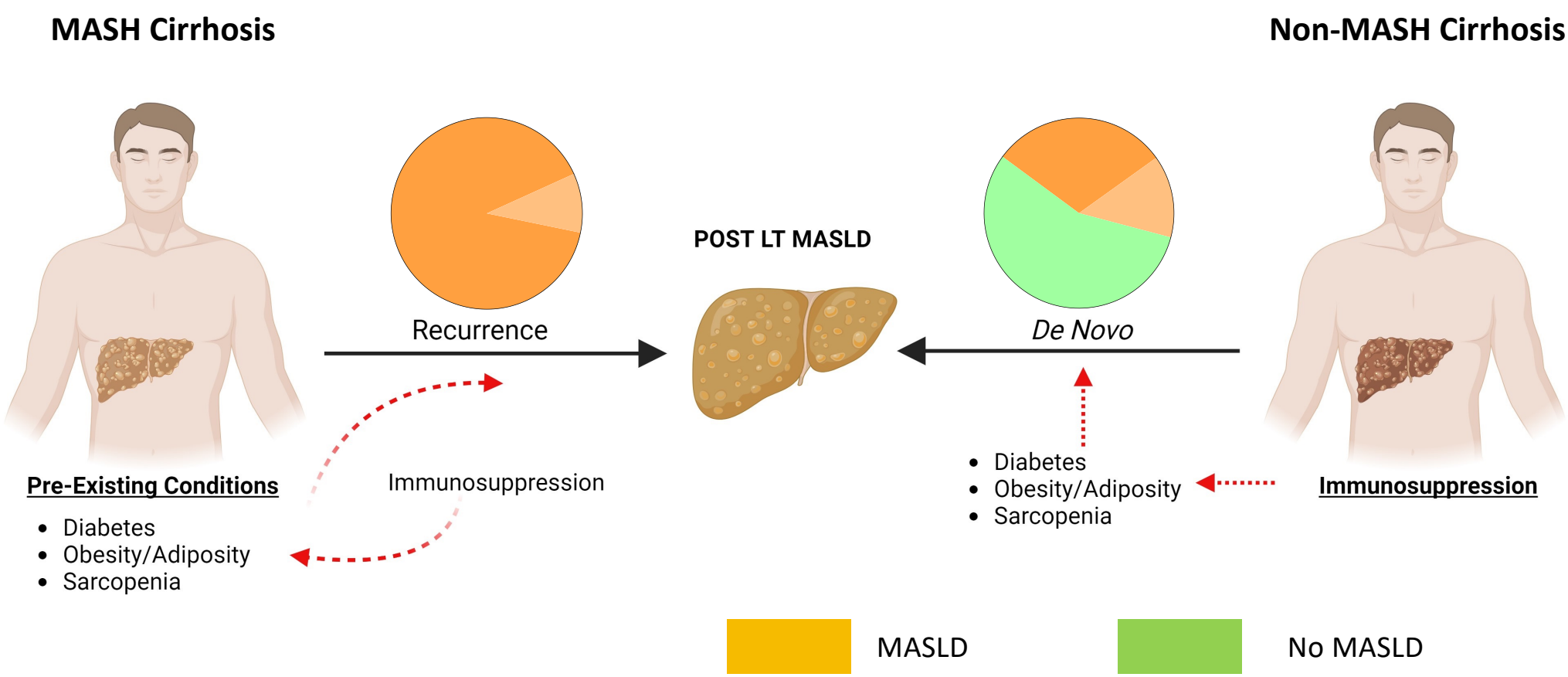
Pre-Existing Conditions

- Diabetes
- Obesity/Adiposity
- Sarcopenia

Recurrence Vs. De Novo MASLD Following Transplant



Recurrence Vs. De Novo MASLD Following Transplant



Fibrosis Progression is Accelerated After Transplant

Bhati et. al. Transplantation 2018

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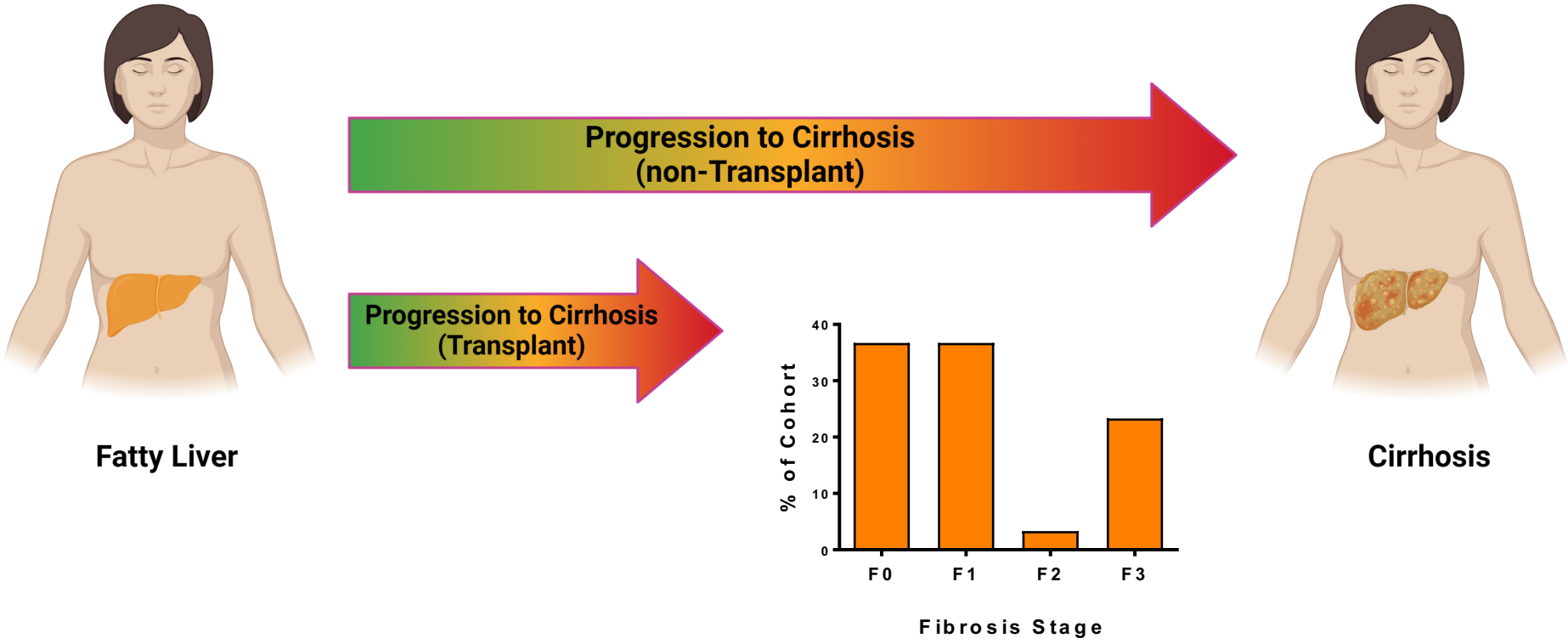
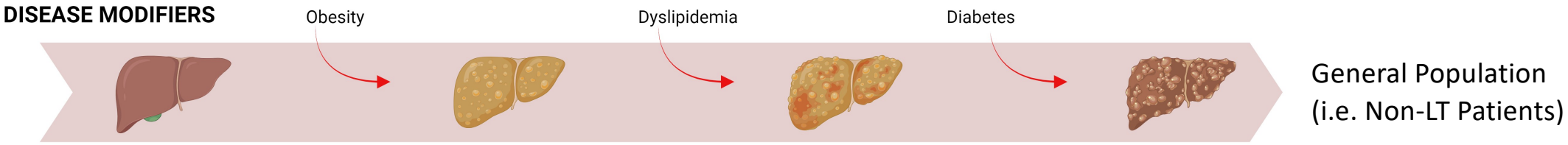


Bhati et. al. Transplantation 2018

Understanding Rationale for Study Design



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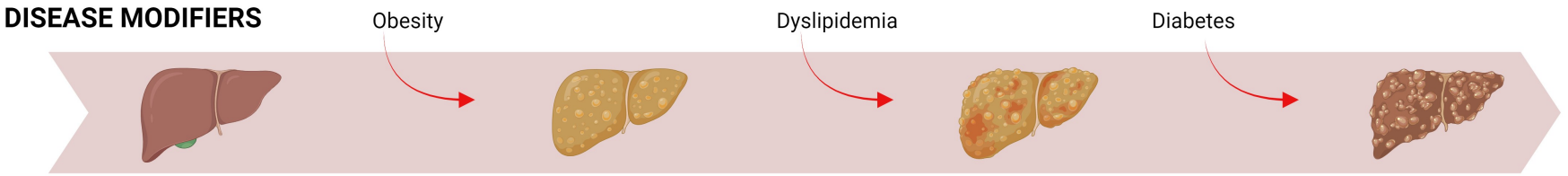
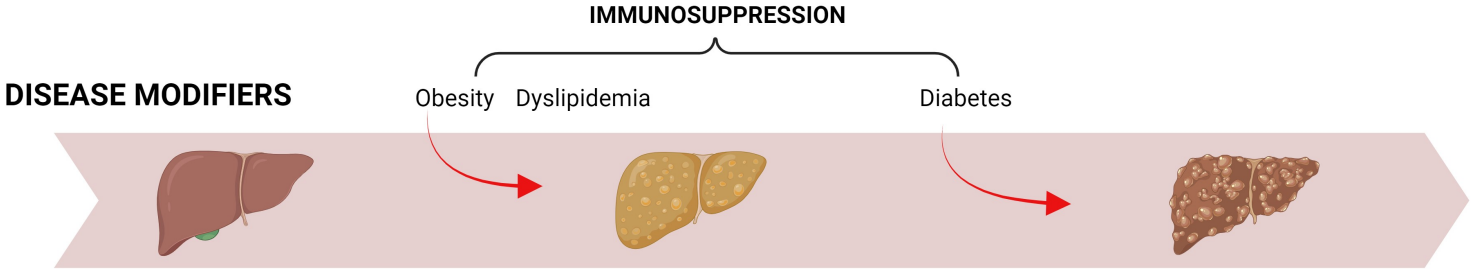
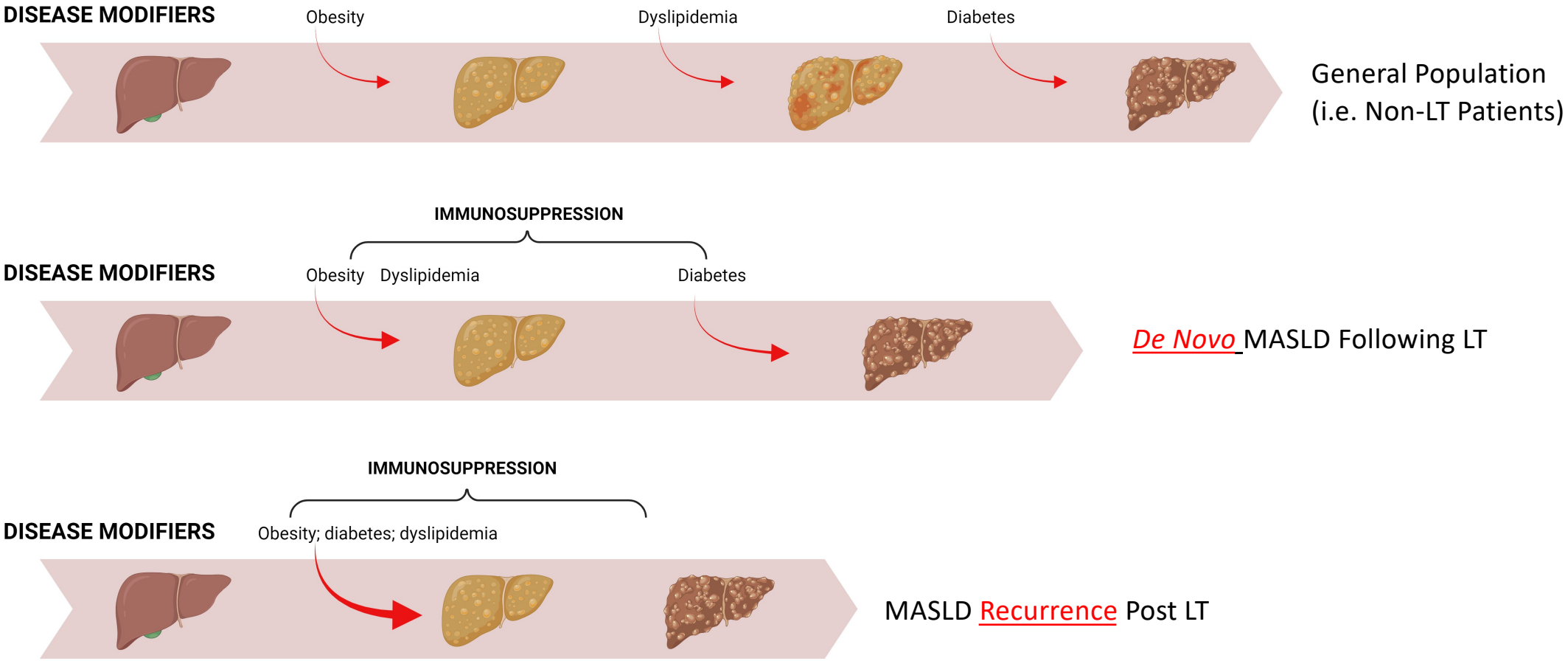


General Population
(i.e. Non-LT Patients)

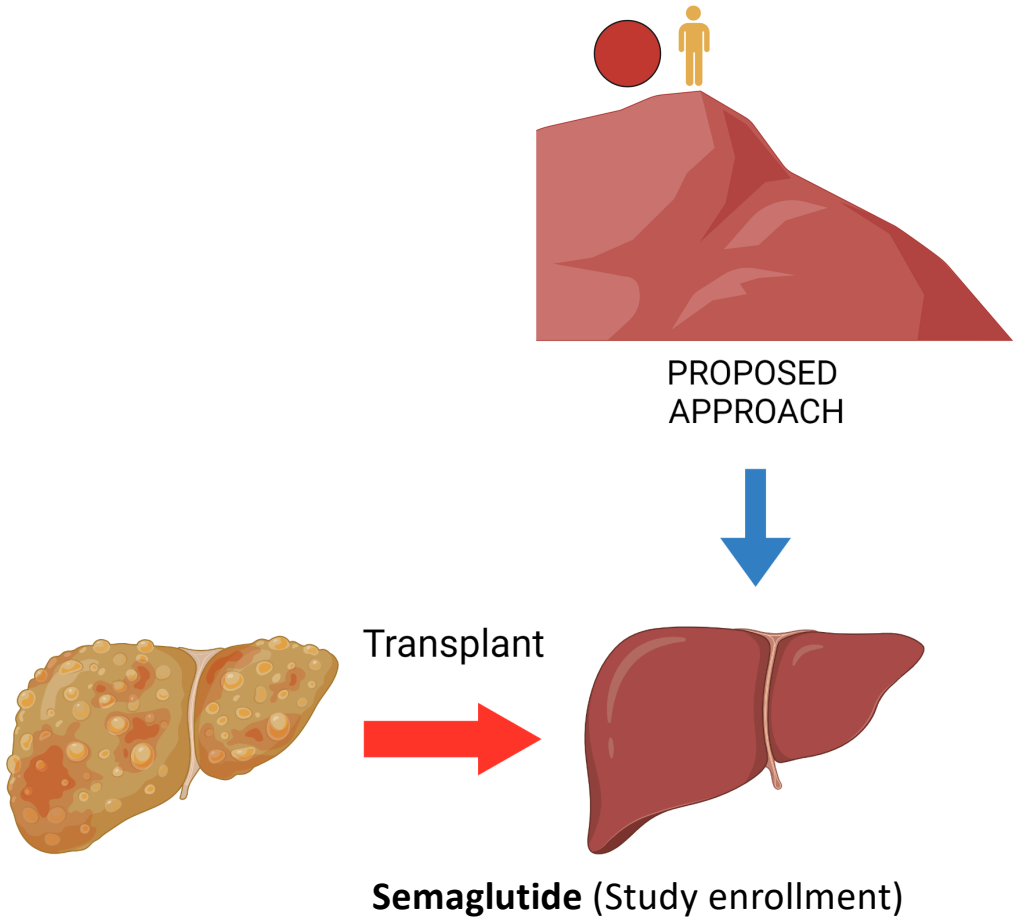


De Novo MASLD Following LT

Understanding Rationale for Study Design



Proposed Study Designs – Prevention Vs. Occurrence



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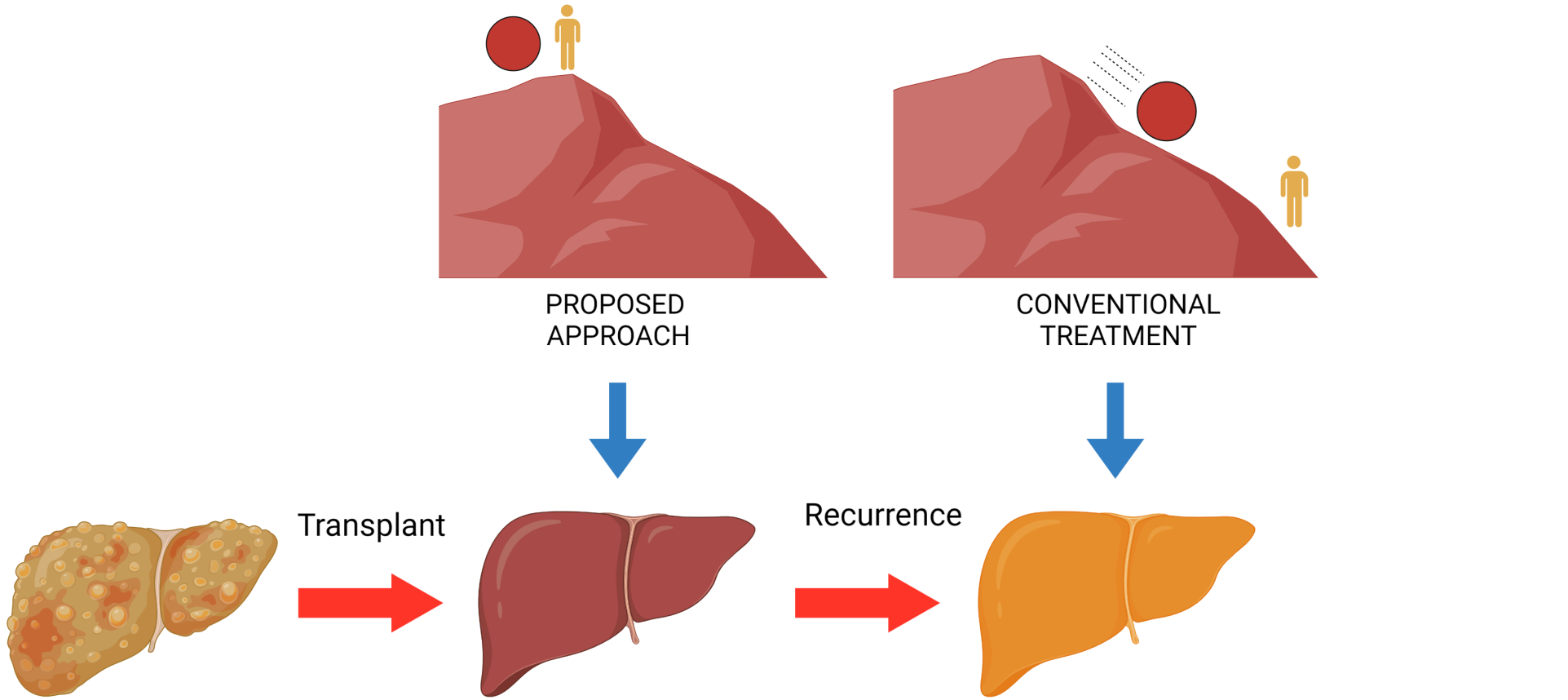
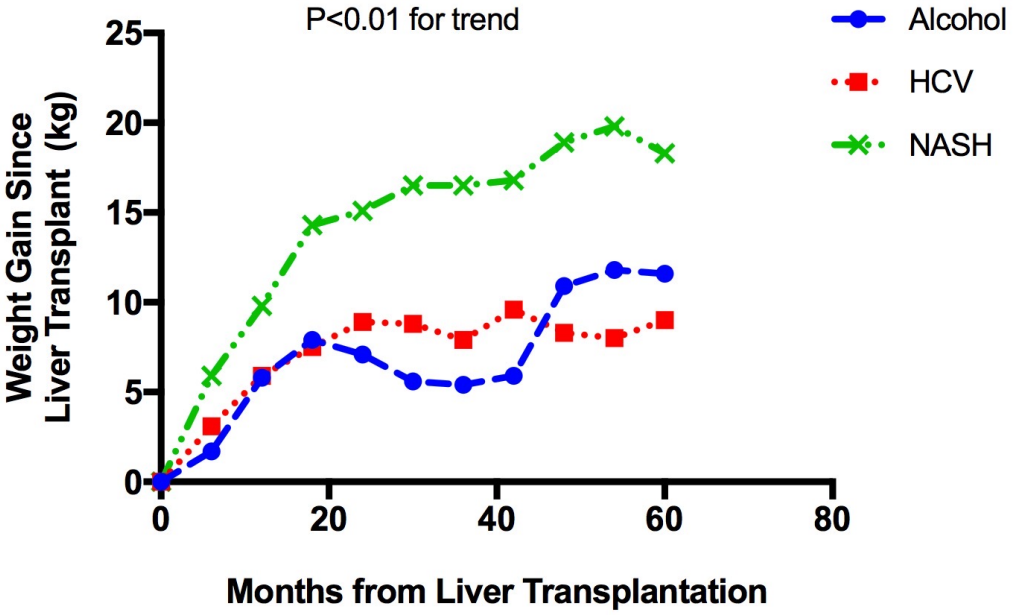
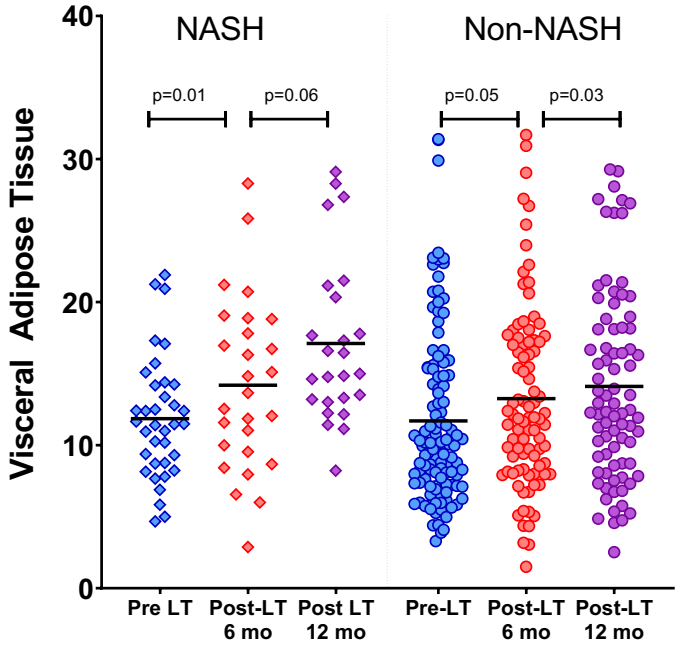


Special Consideration Specific to Liver Transplant Recipients

Disproportionately Higher Metabolic Risk in Patients Transplanted for MASH Cirrhosis

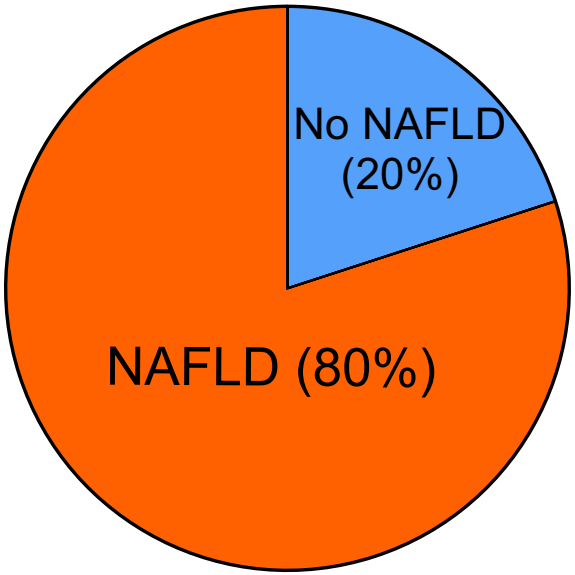
Routine societal approaches to weight loss is not effective in transplant patients



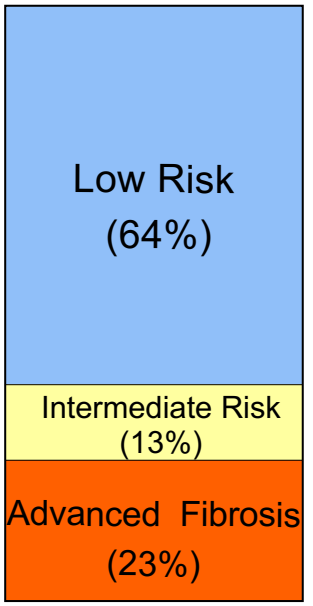


Hassouneh et. al. Transplant 2023

Negative Impact of the Environment on MASLD



NAFLD Prevalence
(~25-30% in general population)

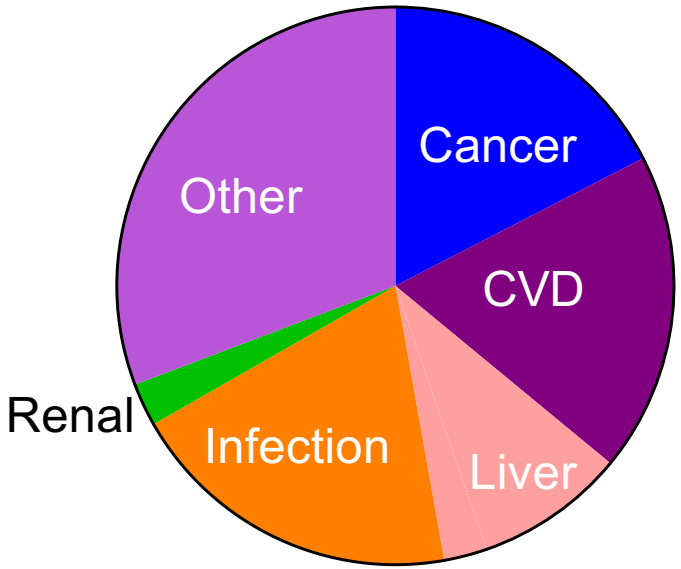


NAFLD Severity
(<1% advanced fibrosis in general population)

Siddiqui et. al. Clin Gastro Hep 2019

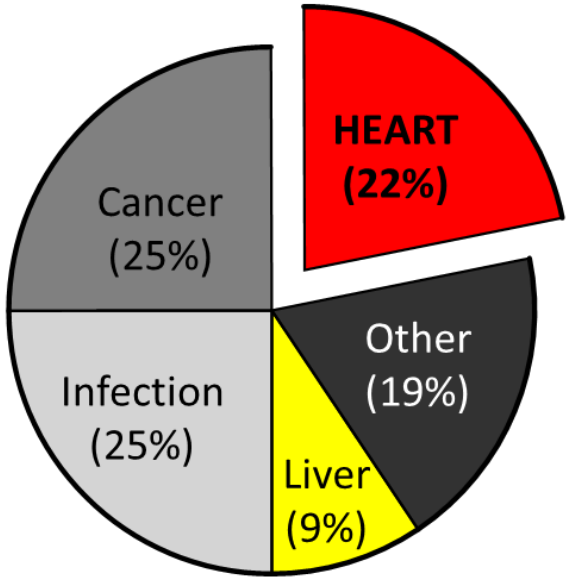
Liver is a Significant Contributor to Overall Mortality After Liver Transplantation

Multicenter Consortium (NailNASH)



Rinella et. al. Clin Gastro Hepatol 2022

Single center Experience (VCU)

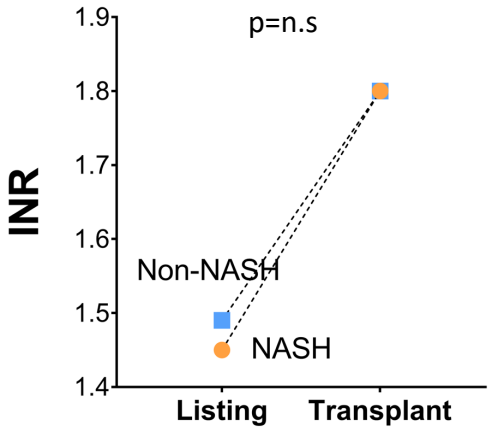


Bhati et. al. Transplantation 2018

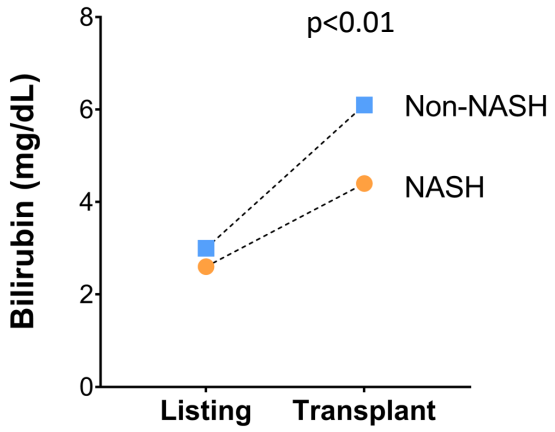
Components of MELD Score As Driver of Transplant

MELD SCORE

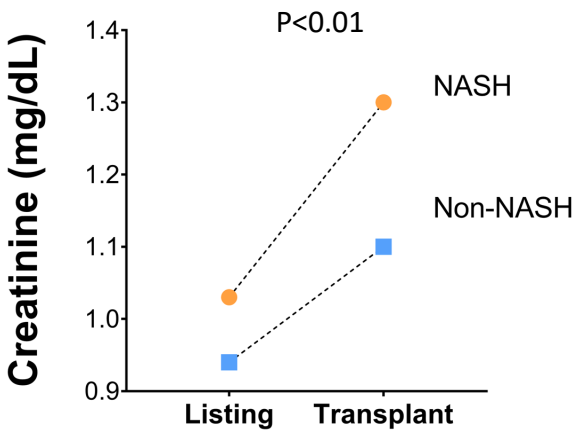
International Normalized Ratio (INR)



Bilirubin



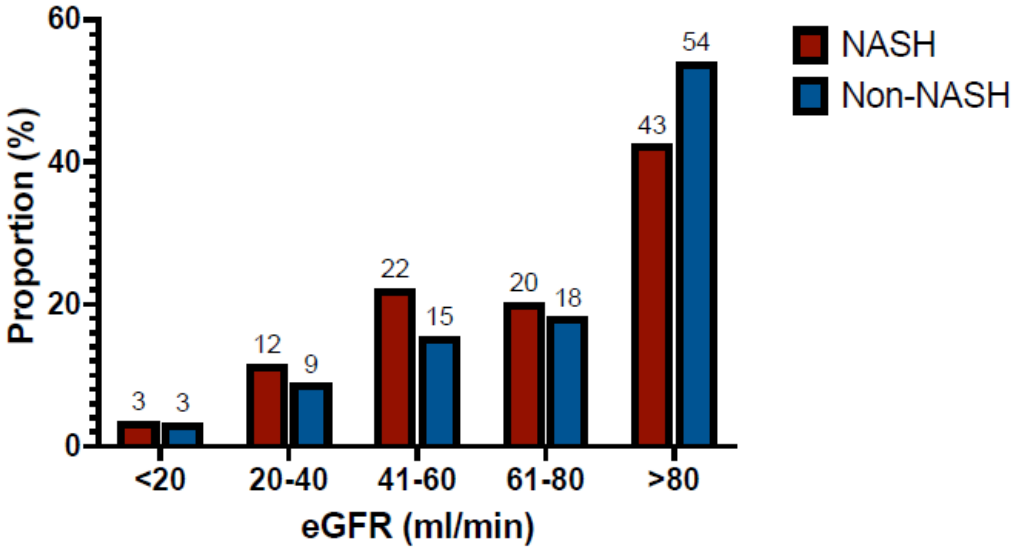
Creatinine

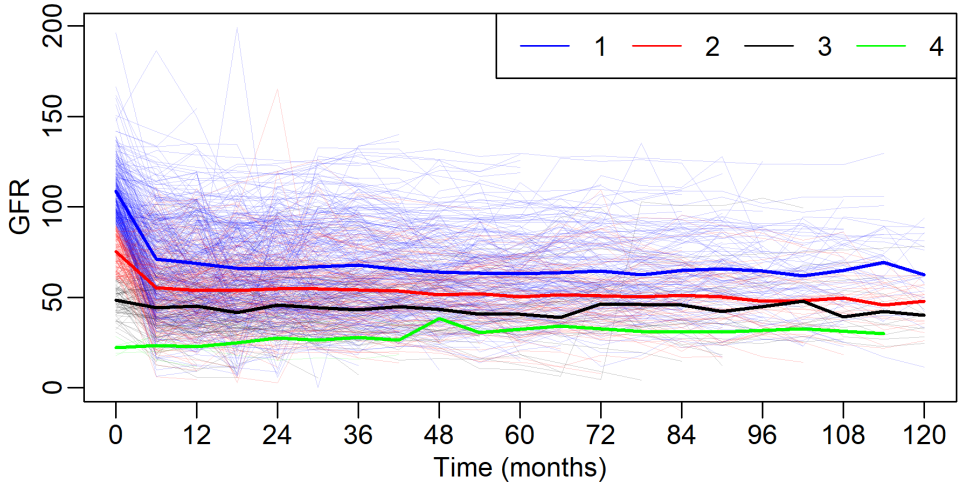


Lim et. al. J Hepatol 2023

Renal Insufficiency is Common In Transplant Recipients, Particularly in Patients Transplanted for MASH Cirrhosis

80% of patients transplanted for MASH cirrhosis has GFR < 60 mL/min/1.73m^2



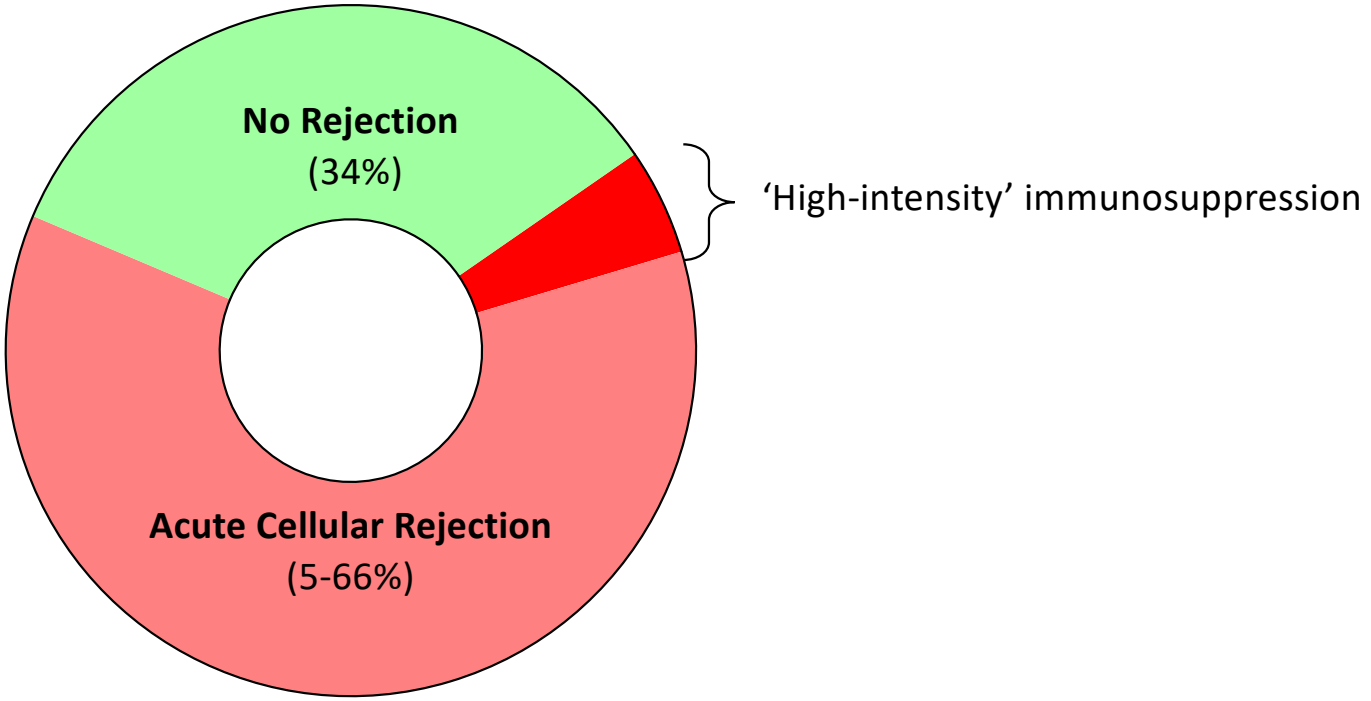


Lim et. al. J Hepatol 2023

Hassouneh et. al. Liver Transplant 2022

Rejection in Liver Transplant Recipients

Meta-analysis 34 RCTs of immunosuppressive regiments

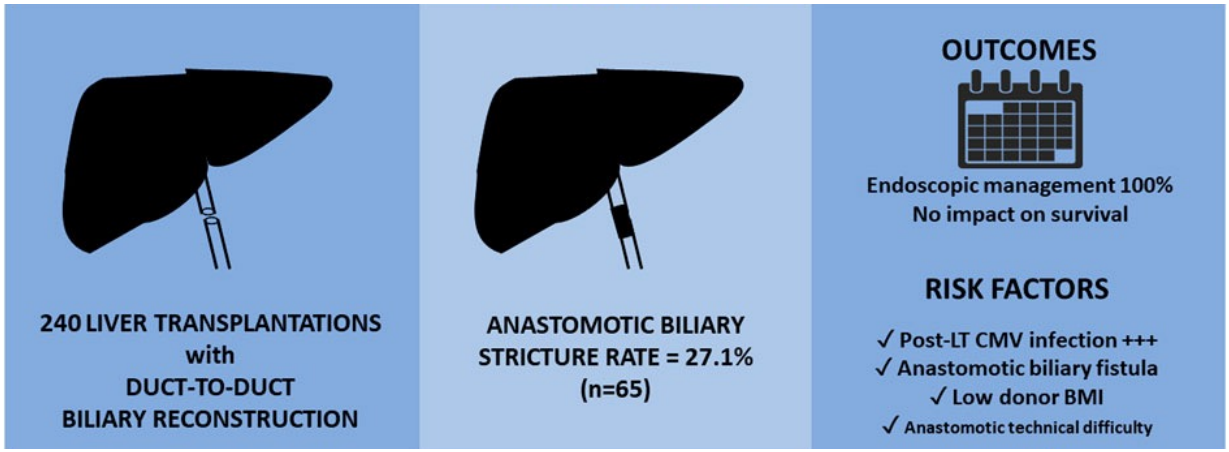


Rodriquez-Peralvarez et. al. Transp Int. 2016

Study Participation and Rejection in Transplant Recipients

- Acute cellular rejections within 3 months should be excluded
- Development of rejection during clinical trials should lead to withdrawal from clinical trial
- Patients with chronic rejections should be excluded

Anastomotic Biliary Strictures are Common Following Transplant



- MRCP should be done at study entry
- Anastomotic biliary strictures that develop during study enrollment should be treated according to best practices
- As anastomotic strictures do not impact survival, patients can continue with study

Georges et. al. Transpl Int. 2022

Medical Consideration for Clinical Trials

- Drug-drug interactions
- Transplant for high-risk cancers (metastatic colon cancer, down-staged HCC, cholangiocarcinoma)
- Immunosuppression monitoring
- Impact on overall metabolic burden

Key Summary Points

- MASH cirrhosis is rapidly growing indication for liver transplantation (LT)
- Occurrence (recurrence/de novo) MASLD is high with accelerated fibrosis progression
- Non-pharmacological interventions are not effective in LT recipients
- Trial design in post-LT MASLD need to account LT physiology (i.e. rejection, renal dysfunction, weight gain, etc.) with opportunity to innovate

Acknowledgements

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Thank You for Your Attention