Alcohol related liver failure-evidence based management in 2022

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Introduction: Alcoholic Hepatitis

- Life-threatening form of liver failure that occurs in patients with sustained heavy alcohol use
  - Rapid onset or worsening of jaundice, liver synthetic dysfunction, and features of hepatic decompensation, including ascites, encephalopathy, and portal hypertensive bleeding
  - Mortality up to 50% at 28 days and up to 70% at 90 days

- Frequently the first clinical presentation of alcohol-related liver disease

Introduction: Alcoholic Hepatitis

EARLY SYMPTOMS OF ALCOHOLIC HEPATITIS

NAUSEA

STOMACH PAIN AND CRAMPING

LACK OF ENERGY

REDUCED APPETITE

WEB-LIKE BLOOD VESSELS ON THE SKIN

UNEXPLAINED WEIGHT LOSS

DARK-COLORED URINE

LATE SYMPTOMS OF ALCOHOLIC HEPATITIS

YELLOWING OF THE EYES AND/OR SKIN

BRUISING EASILY

CONFUSION OR DIFFICULTY THINKING STRAIGHT

PALE OR CLAY-COLORED STOOLS

HAND TREMORS

REDNESS OF THE PALMS OF THE HANDS

A BUILDUP OF FLUIDS IN THE LEGS AND/OR ABDOMEN

ENLARGED LIVER

People with this condition may be more prone to infections of the urinary tract, lungs, and more.

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Alcoholic Hepatitis in the era of COVID 19

Alcoholic Hepatitis in the era of COVID 19
FACT or FICTION?

- Alcohol sales went up by 70% in the United States during the pandemic
- 51% increase in overall incidence of AH requiring hospitalization
- 69% increase in hospitalizations for AH after implementation of the stay-at-home orders
- 100% increase in patients under the age of 40
- 125% increase of male patients admitted with this diagnosis during the COVID-19 pandemic

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- **125% increase of female patients admitted with this diagnosis during the COVID-19 pandemic**

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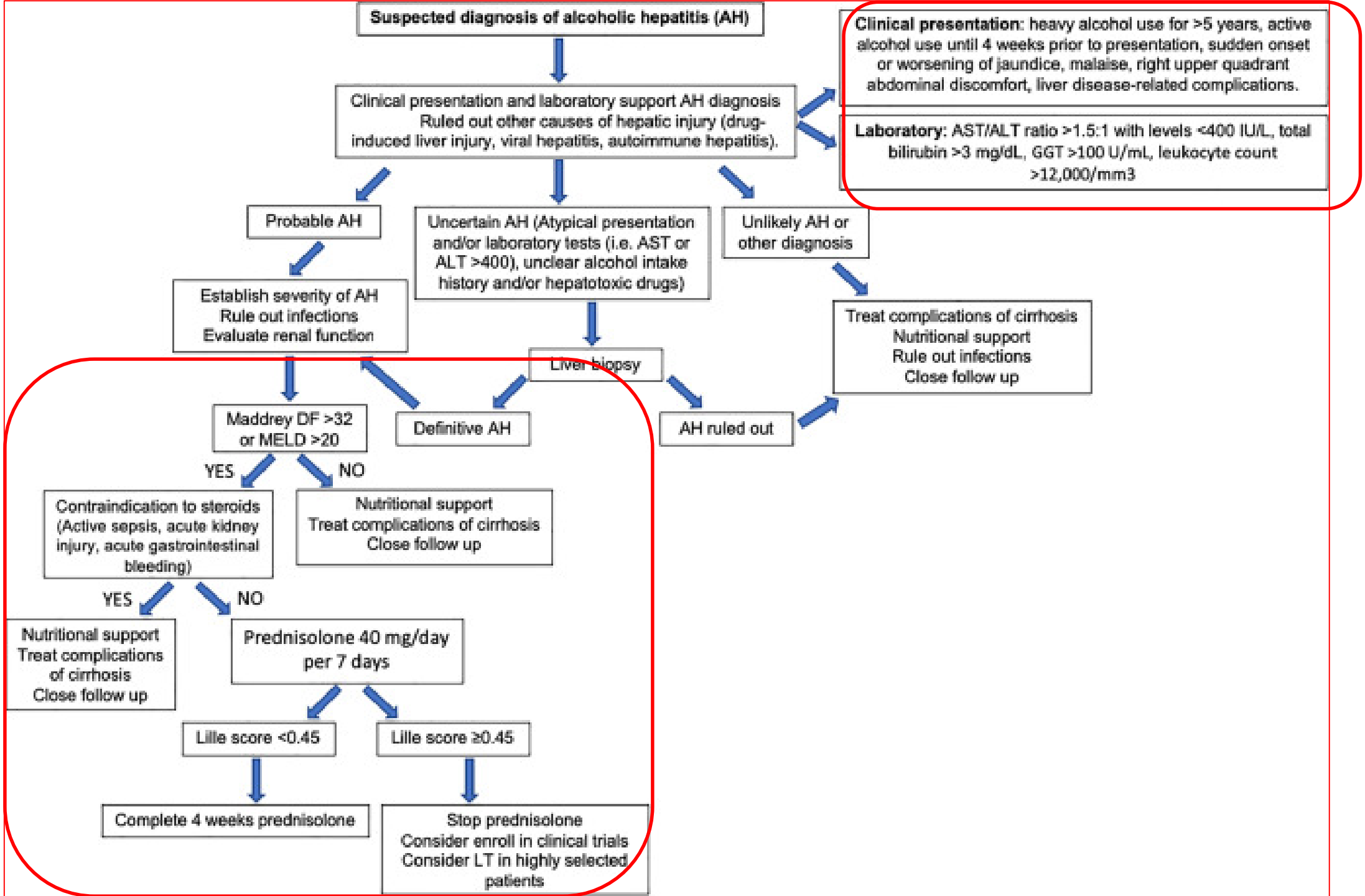

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All of the Scores

- MELD Score (Meld Na)
  - Model for end stage liver disease
    - Factors – dialysis at least twice a week, Cr, total bilirubin, INR, Na
    - Helps prognosticate 90 day mortality in patients with acute liver failure
    - Used for transplant planning and mortality in alcoholic hepatitis

    - *hyponatremia is a sign of excess vasopressin secretion and is a predictive of poor survival in patient with cirrhosis. MELD Na improved prediction of mortality in patients with cirrhosis

- Maddrey Discriminant Function
- Lille Score

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All of the Scores

- MELD Score (Meld Na)

- Maddrey Discriminant Function
  - Used to predict disease severity in patients with alcoholic hepatitis
  - Gives recommendation for steroid treatment
    - Factors: PT and Bilirubin
  - Score >32 indicates potential benefit from steroid administration

- Lille Score

-The Lille Model risk stratifies patients already receiving steroids for alcoholic hepatitis treatment for 7 days to predict which will not improve and should be considered for other management strategies. All values besides 7-day bilirubin are taken from admission.

-Factors included- Albumin, Age, TBil on admission, TBil at Day 7, Creatinine and PT

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Treatment Options

- **Pharmacotherapy remains limited**
  - 50% cannot tolerate or do not respond to corticosteroid therapy
  - Up to 20% present with co existing infection of GI bleeding precluding corticosteroid use

- Molecular Adsorbent Recirculatory System (MARS)

- More recently, early liver transplantation (LT) has been used in carefully selected populations showing 3-year survival rates equivalent to those for other chronic liver diseases

DURECT Clinical Trial

Study Type :	Interventional (Clinical Trial)
Intervention Model Description:	This is a Phase 2b randomized, double-blind, placebo-controlled, multi-arm, multi-center, parallel design trial.
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Randomized, Double-blind, Placebo-controlled, Phase 2b Study to Evaluate Safety and Efficacy of DUR-928 in Subjects With Alcoholic Hepatitis
Actual Study Start Date :	January 22, 2021
Estimated Study Completion Date :	September 2023

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DUR-928 Mechanism of Action

- DUR-928,is an endogenous sulfated oxysterol that has been shown to bind and inhibit the activity of DNMTs
  - By inhibiting aberrant DNMT activity / DNA methylation this drug modulates crucial cellular activities including those associated with cell death, stress response, and lipid biosynthesis.
  - These modulations may lead to improved cell survival, and reduced lipotoxicity and inflammation.
- Given its proposed mechanism of action there is scientific rationale for investigating it in treatment for diseases such as alcohol-associated hepatitis and NASH.

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DURECT Clinical Trial **Inclusion** Criteria

1. Able to provide written informed consent (either from subject or subject's legally acceptable representative)

2. Onset of jaundice within prior 8 weeks

3. Average daily consumption of >40 (females) or >60 (males) grams of alcohol for 6 months or longer, with < 8 weeks of abstinence before the onset of jaundice. Judgment regarding daily and long-term alcohol use and onset of jaundice will be made by the site investigator.

4. Serum chemistry (as determined by local laboratory):
    1. Serum total bilirubin > 3.0 mg/dL
    2. 50 < AST < 400 IU/L
    3. ALT < 400 IU/L
    4. AST/ALT > 1.5

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DURECT Clinical Trial **Inclusion** Criteria

5. Maddrey's discriminant function ≥ 32 assuming a control prothrombin time of 12 seconds

6. Model for End-stage Liver Disease (MELD) score: 21-30

7. When the diagnosis of AH remains in question, a liver biopsy (if clinically feasible and that subject has no contra-indications) will be required. Historical biopsy is allowed.

8. Subjects must agree to use effective methods to prevent pregnancy while participating in the study.

9. Subjects must agree to participate in an alcohol abstinence support program recommended by the local institution's addiction specialists

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DURECT Clinical Trial **Exclusion** Criteria

1. Subjects taking corticosteroids for a duration over 7 days in the last month
2. Alcohol withdrawal symptoms
3. Active infection
4. Serum creatinine >2.5 mg/dL or eGFR < 60
5. acute kidney injury (AKI) or Hepatorenal syndrome
6. Hemodialysis or continuous veno-venous hemodialysis (CVVH)
7. Uncontrolled active gastrointestinal bleeding
8. Refractory ascites
9. Liver biopsy (if carried out) with findings not compatible with AH
10. Stage ≥3 hepatic encephalopathy by West Haven criteria
11. Any severe concomitant cardiovascular, renal, endocrine, pulmonary, psychiatric disorder, or multi-organ failure

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DURECT Clinical Trial **Exclusion** Criteria

12. Other concomitant cause(s) of liver disease
13. Any active malignancies other than curatively treated skin cancer or any other malignancy within the last five years.
14. Positive Urine Drug Screen except THC and prescription medications
15. Existing or intended pregnancy or breast feeding
16. Participation in another interventional clinical trial within 30 days of Screening
17. History of organ transplantation, other than a corneal transplant
18. Underlying diseases that, in the opinion of the site investigator, might be complicated or exacerbated by proposed treatments or might confound assessment of study drug

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Clinical Arms of the DURECT Trial

Arm	Intervention/treatment
Experimental: DUR-928 (30 mg)	Drug: DUR-928 30 mgIV infusion
Experimental: DUR-928 (90 mg)	Drug: DUR-928 90 mgIV infusion
Placebo Comparator: (Placebo) Sterile Water for Injection	Drug: Placebo+ Standard of Care (SOC)IV infusion

DURECT Trial Outcomes

- Primary Outcome Measures
  - 90-day mortality between active group/s and placebo (SOC) group [Time Frame: Day 90]

- Secondary Outcome Measures
  - 28-day mortality between the treatment groups
  - Occurrence of adverse events or laboratory abnormalities [Time Frame: Day 1 to Day 90]
  - Lille score at Day 7
  - MELD score at Day 28
  - ICU days at Day 28

- Alcoholic liver disease is complex.
- It’s the physical manifestation of a disease that has basis in emotional and psychological distress.
- For patients early with signs of dependence the key is prevention. It is our duty as physicians to identify certain drinking habits as a problem and help with finding treatment of the root cause.

Accelerate AH study- aims

- To inform ongoing debate and policy, data regarding long-term outcomes and how different rates of post-LT alcohol use may affect outcomes are needed.
- Aim 1: Evaluate the comparative effectiveness of early LT versus delayed LT (6-month wait) for severe AH by different rates of post-LT alcohol use.
- Aim 2: Quantify the harm of post-LT alcohol use on graft and patient survival.

Background

- Alcohol-associated liver disease is now the #1 indication for liver transplantation (LT) in the United States.
- Alcohol-associated liver disease accounts for 48% of liver-related deaths in the United States.
- Early LT (i.e. without requiring a minimum period of sobriety) for severe alcoholic hepatitis (AH) was considered controversial till 2 years ago.
- Many centers delay LT eligibility until a specific period of sobriety (e.g. 6-months) is achieved.
- The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH)2 reported acceptable post-LT survival rates (~85% at 2-3 years)

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Accelerate AH study- materials and methods

- Model Overview - Markov-based mathematical model, simulating a virtual trial of severe AH patients offered early LT versus delayed LT –
- Data from ACCELERATE-AH, UNOS, other studies Base Case Population - Based on ACCELERATE-AH cohort (mean age 43, 70% male, median MELD 38, Day 7 Lille 0.82)
- - Patients categorized into 3 possible alcohol use categories after LT: abstinent (no evidence of any alcohol use), slip (alcohol use followed by sobriety), sustained (ongoing alcohol use).
- Interventions - Early LT: listed after determining refractory disease by Day 7 Lille Score, and time for psychosocial and financial evaluation - Delayed LT: listed after achieving 6 months of abstinence
- Model Outcomes - Life expectancy, measured in life-years Sensitivity/Scenario Analyses - Extreme scenarios (e.g. all early LT patients have sustained alcohol use after LT, and all delayed LT patients are abstinent) - By UNOS region - Different delayed LT policies (i.e. 1-month, 3-month)

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Results

Table 1. Life Expectancy by Offering Early LT versus Delayed LT: Base Case and by Varying Rates of Alcohol Use

	Life Expectancy (Life Years)		
	Early LT	Delayed LT	Net Difference (Early versus Delayed LT)
Base Case[a]	6.55	1.46	5.09
Scenario 1[b]	3.62	2.30	1.32
Scenario 2[c]	6.55	1.81	4.74
Scenario 3[d]	10.85	1.46	9.39

[a]**Base Case:** equivalent alcohol use after LT for early vs. delayed LT
[b]**Scenario 1:** all patients after early LT have sustained alcohol use vs. no alcohol use after delayed LT
[c]**Scenario 2:** no patient offered delayed LT has alcohol use in 6 month pre-LT period
[d]**Scenario 3:** no patient offered early LT has alcohol use after LT

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Results

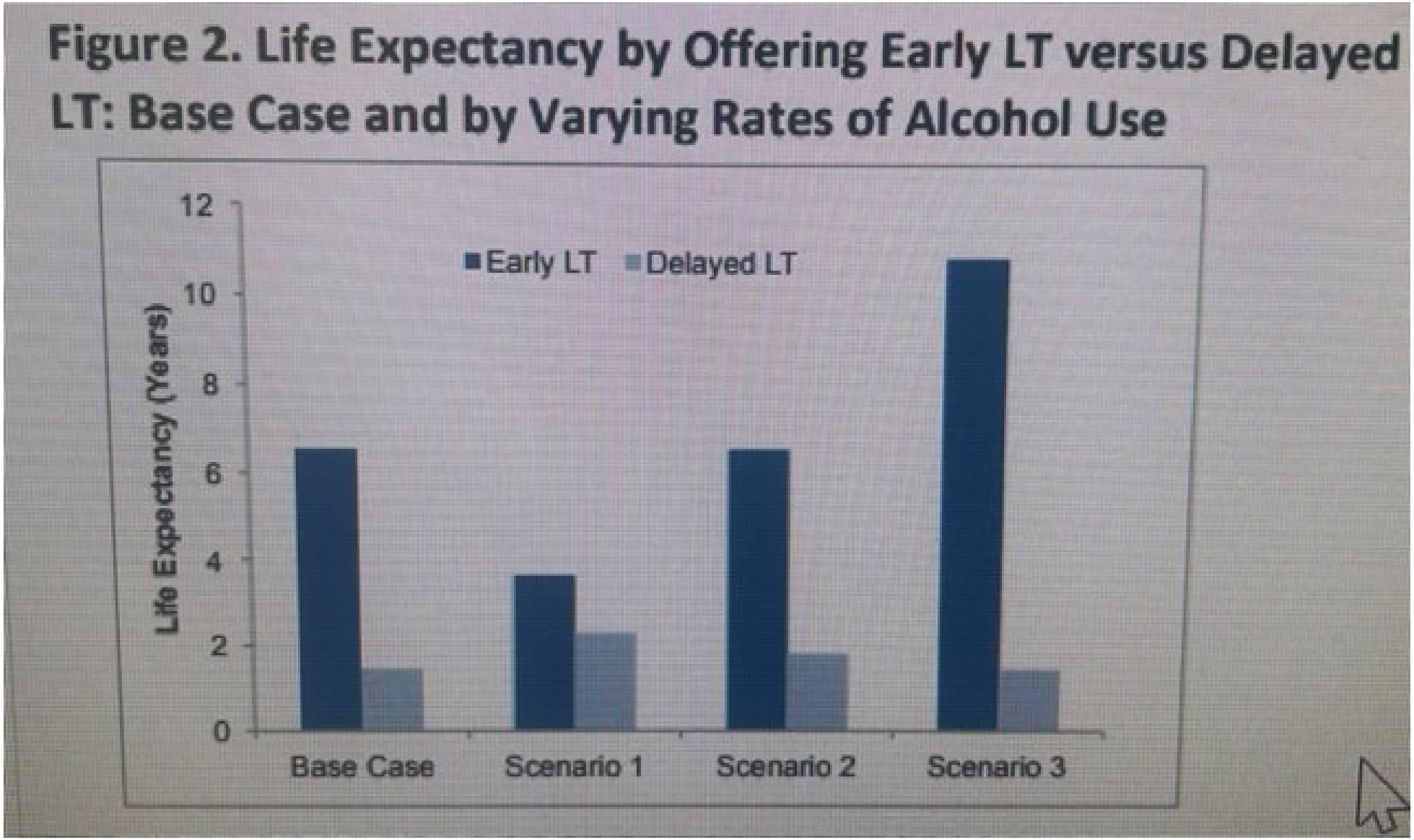
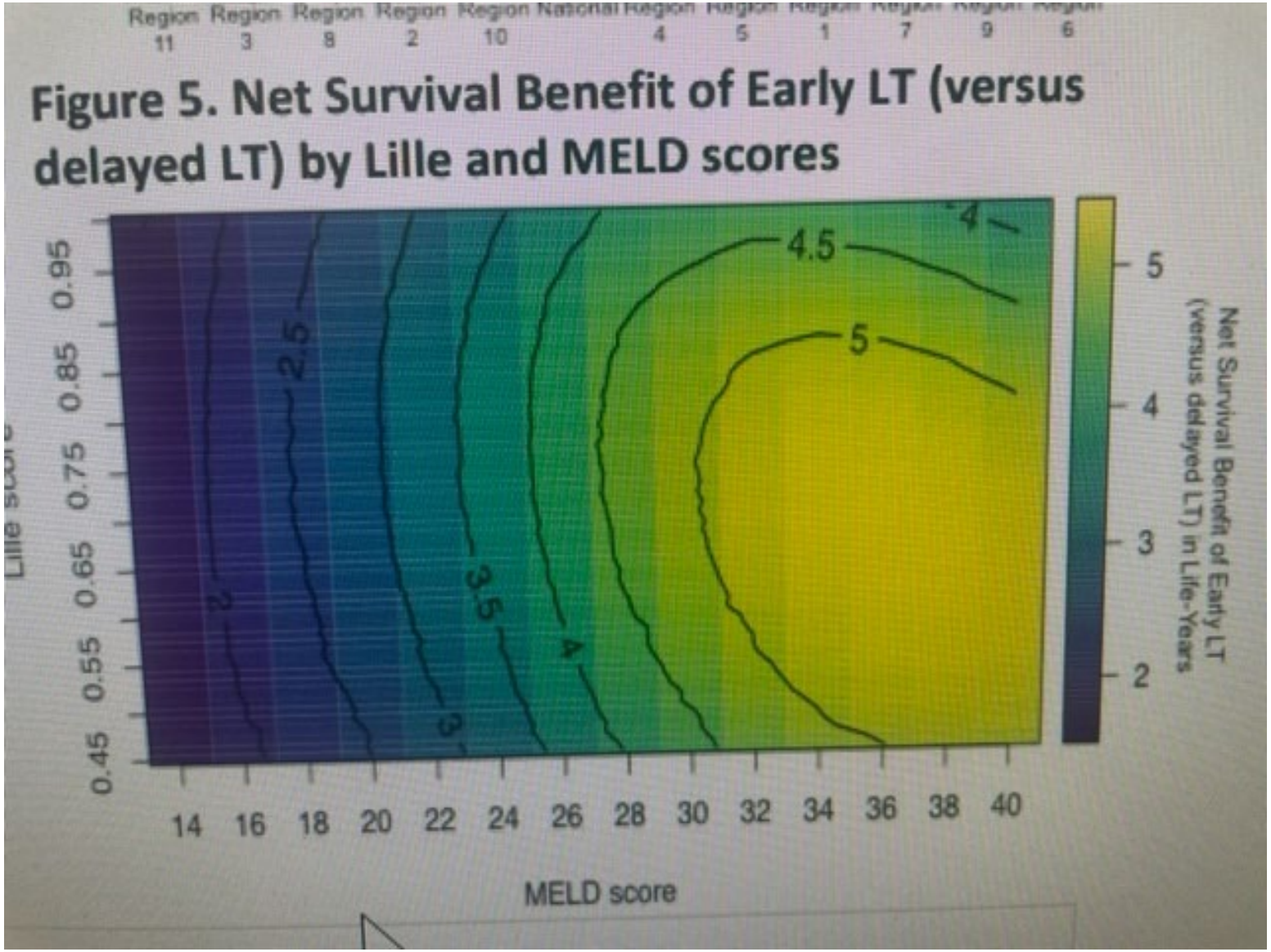


Figure 2. Life Expectancy by Offering Early LT versus Delayed LT: Base Case and by Varying Rates of Alcohol Use
Early LT
Delayed LT
Life Expectancy (Years)
12
10
8
6
4
2
0
Base Case
Scenario 1
Scenario 2
Scenario 3

Results


Region 11
Region 3
Region 8
Region 2
Region 10
National
Region 4
Region 5
Region 1
Region 7
Region 9
Region 6
Figure 5. Net Survival Benefit of Early LT (versus delayed LT) by Lille and MELD scores
Lille score
0.45
0.55
0.65
0.75
0.85
0.95
2
2.5
3
3.5
4
4.5
5
14
16
18
20
22
24
26
28
30
32
34
36
38
40
MELD score
Net Survival Benefit of Early LT (versus delayed LT) in Life-Years
2
3
4
5

Conclusions

- An early LT policy (versus delayed LT) maintains survival benefit irrespective of any estimated risk of sustained alcohol use post-LT
- Sustained alcohol use post-LT significantly reduced but did not eliminate early transplant benefit, highlighting the need for prevention and treatment for post-LT alcohol use.
- Early LT (versus delayed LT) provided survival benefit across all simulated scenarios, all UNOS regions, and combinations of Lille and MELD scores. –
- These findings support the use of early LT as definitive therapy for severe AH.

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Summary

- Offering early LT provided 4.49-fold survival benefit over delayed LT (6.55 vs. 1.46 lifeyears).
- Net survival benefit of early LT was highest with Lille 0.50-0.82, and MELD≥32.
- In a patient offered early LT, life-expectancy was 10.85 years with post-LT abstinence versus 3.62 years with sustained alcohol use post-LT, resulting in 7.23 life-years lost. –
- Sustained alcohol use post-LT results in 67% loss of life-years gained by early LT (compared to complete abstinence).

Methodist and Liver Transplantation for Alcohol Related Liver Disease

- End Stage Liver Disease
- Acute on Chronic Decompensation
- Acute Alcoholic Hepatitis

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General Criteria

- Sobriety Issues-

A. End stage Liver Disease- 6 months with participation in recovery program

B. Acute on Chronic Decompensation- 6 months if decompensation is from recurrent alcohol use <6 months if decompensation is from concurrent infection/GI bleed/Circulatory injury

C. Alcoholic Hepatitis- No definite duration of Sobriety but……

Psychosocial Criteria for Transplanting Alcoholic Hepatitis

- Not a repeated relapsing pattern
- Severe first episode
- Strong Family Support
- Functioning previously (working /lack of DWI)
- No evidence of polysubstance use
- No previous documentation of medical counseling regarding ETOH cessation.
- Commitment to enrollment in a lifelong recovery program

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Medical criteria for transplanting patients with alcoholic hepatitis

- Young age (<65y)
- Lack of significant comorbidities
- Absence of active infection (bacteremia)
- Unresponsive to Steroids or medically contraindicated
- MELD >28

Medical Management of AH/AOCH- Referring Hospitals

- IV Albumin (when suspecting HRS)- 25g every 6 hours.
- Broad spectrum IV abx
- Frequent paracentesis (with IV albumin) – SBP vigilance
- Keep MAP >65 (albumin/midodrine/norepinephrine
- Close communication with transplant center
- Early verification of insurance benefits and family support.
- Pulling the trigger if above medical/Psychosocial criteria are met.

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Medical Management of AH/AOCH- Methodist

- Initiation of CVVH
- Keeping MAP over 70
- Multidisciplinary ICU/Progressive Care
- TEG guidance for placement of Quinton Catheters
- Consideration of MARS
- Consideration of Clinical Trial
- Consideration of OLTX

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Molecular Adsorbent Recirculatory System (MARS)

- MARS combines traditional continuous renal replacement therapy (CRRT) technology with large protein-bound particle removal via albumin dialysis.
- It removes ammonia, bilirubin, bile acids, aromatic amino acids, nitric oxide, tryptophan, copper, creatinine, protoporphyrin, urea, and diazepam.
- Human albumin cleans protein-bound toxins, while the bicarbonate-based dialysate binds other water-soluble elements.
- By supporting the injured liver and decreasing the encephalopathy risk, MARS gives the liver time to regain normal function.
- Patient selection and timing are crucial.
- Standard indications for MARS include ALF caused by drugs or toxins, grade 1 or higher encephalopathy, INR above 2.0, and pH below 7.3 in the absence of acute kidney failure.
- The MARS protocol is developed in collaboration with a hepatologist, a nephrologist, critical care specialists, and nursing staff.
- The recommended treatment mode is intermittent, with treatment lasting 12 hours daily for 5 consecutive days. CRRT may be used between MARS sessions to support renal function and continue filtration of smaller and mid-range molecular substances (particularly ammonia).

Summary

- Alcohol related liver disease is the most common indication for Liver Transplantation.
- Early transplantation of patients with severe liver failure leads to good outcomes and survival.
- Some Patients with Alcoholic hepatitis may greatly benefit from early referral and consideration for OLTX.
- Medical and psychosocial criteria are well developed and can be useful guides for referral