Management of a patient with cirrhosis on the transplant wait list.

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Outline

- Introduction to LT
- Wait list
  - Who gets on it
  - Risk assessment
- Case scenario of typical patient
- Problems faced while on wait list
- Management while waiting
- Optimization
- Conclusions

A brief introduction to Liver transplant…..

Ultimate treatment for end stage liver disease / acute liver failure

> 5000 LT performed annually in Europe

Total > 140000 worldwide

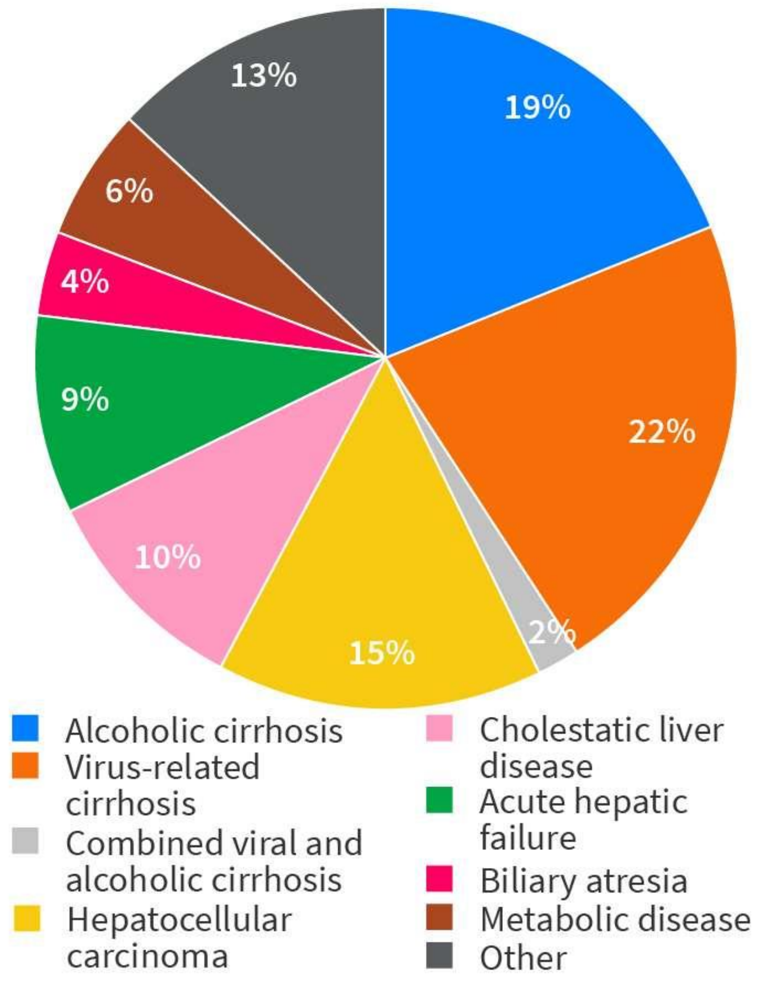
Survival at :

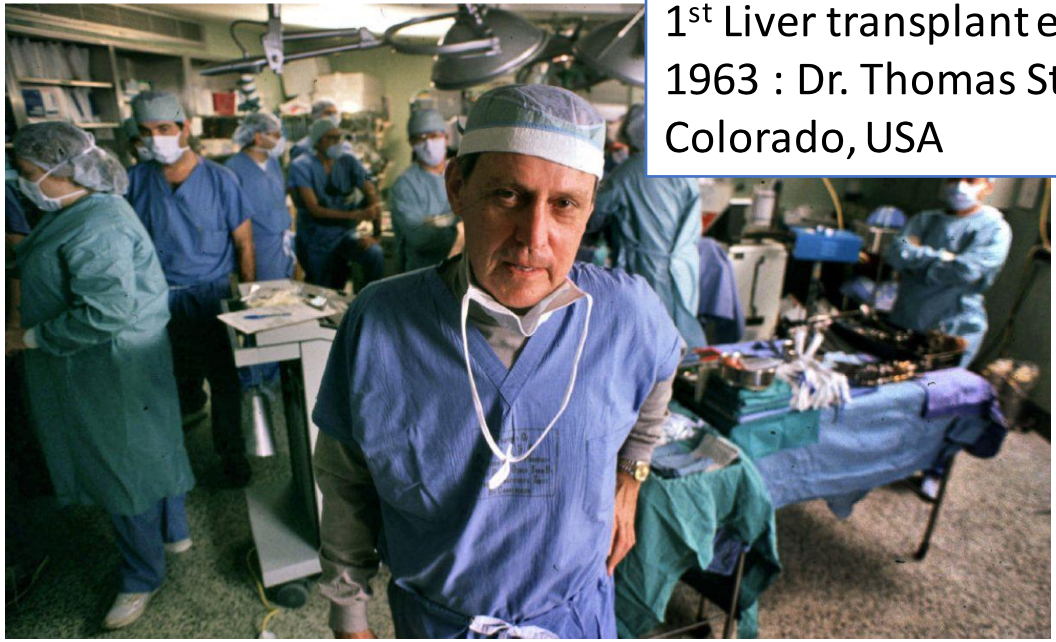
- 1 year 90%,
- 5yrs 80%
- 10yrs 71%

Cadaveric or Live liver donors

Death while on waiting list ~ 20%

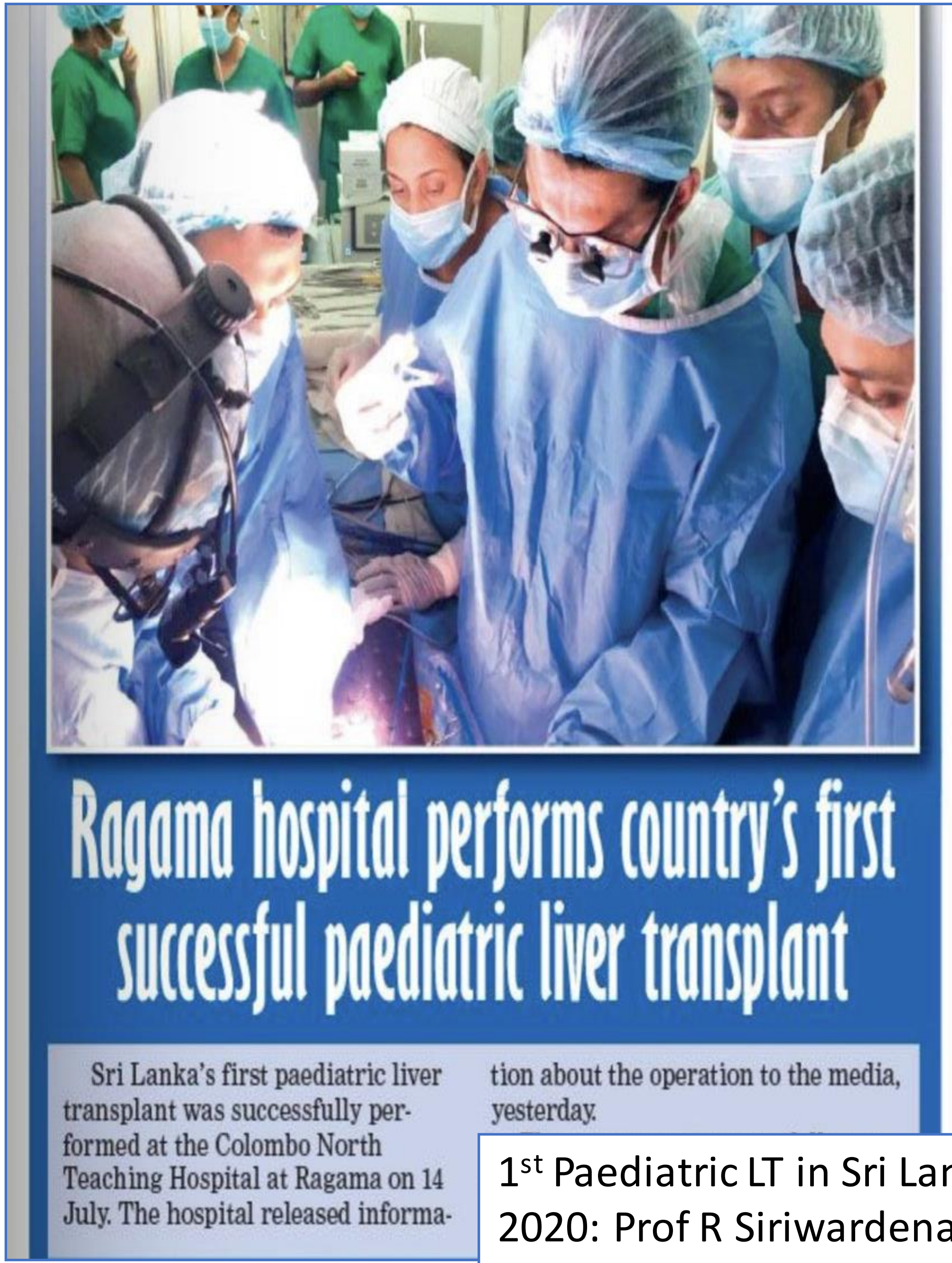
Indications for LT





1st Liver transplant ever
1963 : Dr. Thomas Starzl
Colorado, USA

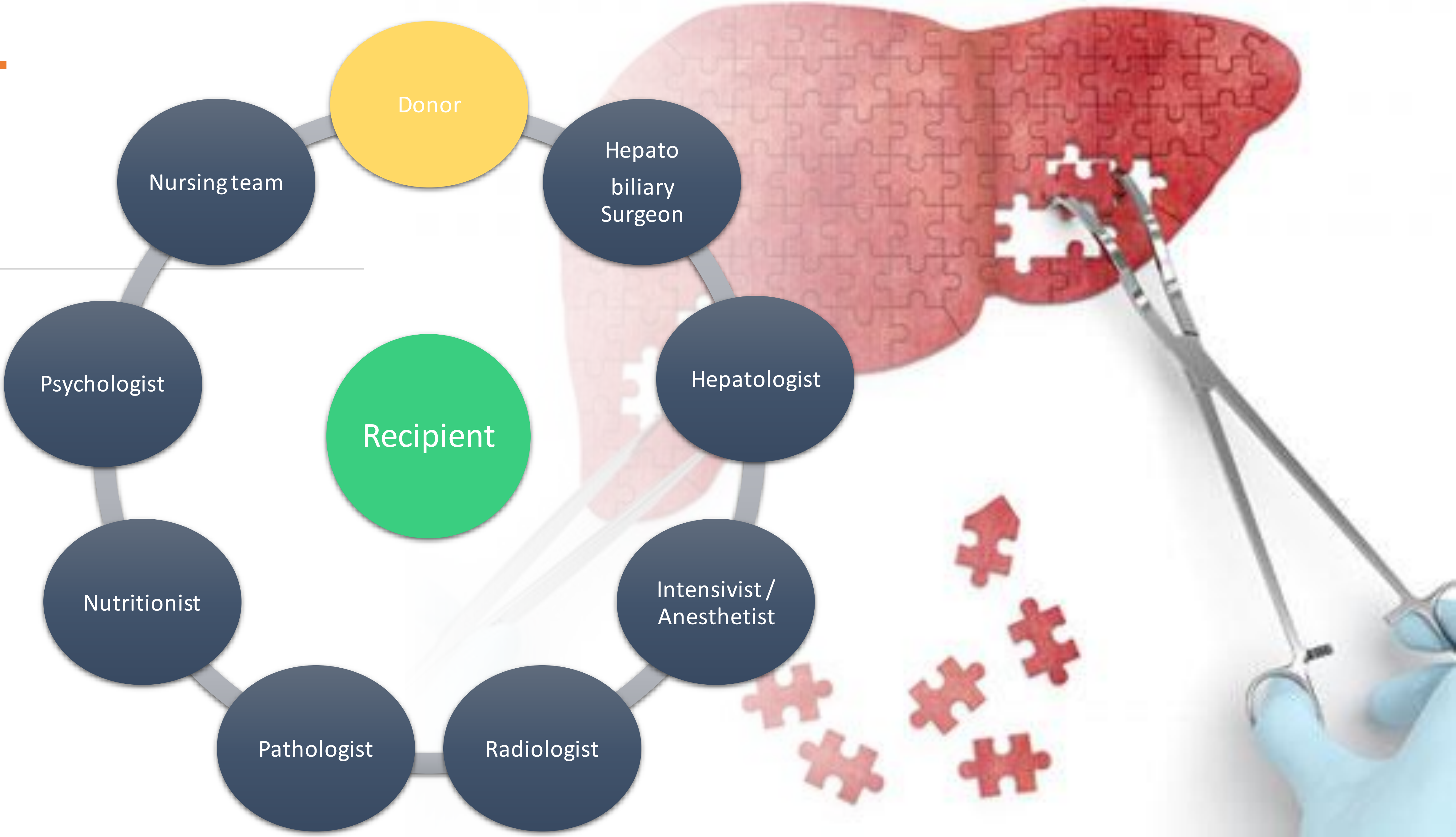
1st LT in Sri Lanka
2010: Prof M Wijeratne &
team, NHSL Colombo



Ragama hospital performs country's first successful paediatric liver transplant

Sri Lanka's first paediatric liver transplant was successfully performed at the Colombo North Teaching Hospital at Ragama on 14 July. The hospital released information about the operation to the media, yesterday.

1st Paediatric LT in Sri Lanka
2020: Prof R Siriwardena
CNTH Ragama


Donor
Hepato
biliary
Surgeon
Hepatologist
Intensivist /
Anesthetist
Radiologist
Pathologist
Nutritionist
Psychologist
Nursing team
Recipient

LT Wait List

Include:

1. ALF
2. Decompensated CLCD
3. HCC with compensated CLCD

Shortage of livers

Recipient blood group

Difficult to predict

Many potential risks while waiting

Multiple listings

De-listing

GOAL:

to prevent wait list mortality and drop out

Risks
Infection
Bleeding
CVS events
HE
Hyponatraemia
Ascites
HCC
Poor Nutrition
Alcohol relapse
Psychological issues
Renal dysfunction

Meet our typical patient:

- 59yr old Male from Veyangoda
- Alcohol related liver disease (CTP class C , MELD–Na score 17)
- Abstinent 1yr
- Co-morbidities: DM (4yrs)
- <u>Added to wait list : Feb 2020</u>
- Recurrent admissions with HE x2, UGI bleed x1 [grade 2 varices, mild gastropathy]
- Last admission: April 2021: Massive ascites, jaundice, poor appetite, BMI 20.4kg/m^2
- Large volume paracentesis done with albumin cover – No SBP/AKI/HE
- Diuretics adjusted; Nutrition optimized
- Routine follow up

How to risk assess those on wait list for LT?

CTP

MELD

MELD-Na

Child-Turcotte-Pugh

1964/1972

Bilirubin

INR

Albumin

HE

Ascites

Model for End stage Liver disease

2001

Bilirubin

INR

Creatinine

Model for End stage Liver disease - sodium

2016

Bilirubin

INR

Creatinine

Na+

2 Minute Medicine®	Child-Pugh Score		2minutemedicine.com
Factor	**1 point**	**2 points**	**3 points**
Total bilirubin (μmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	**Class B**	**Class C**
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Table I. Child-Pugh score.

MELD/MELD-Na

Range 6-40

Age >12yrs

"Sickest first" –Justice system

Best transplant survival MELD >15

Waiting time for intermediate MELD > 1yr

Including S.Na increases predictivity

CTP+MELD Na = superior to MELD alone

But there are problems:

- Nutrition not included
- Creatinine variance
- INR in anticoagulated pts

MELD exceptions:

- HCC,
- Hepatopulmonary syndrome,
- Portopulmonary HTN,
- Cholangio Ca

Samuel D, Coilly A. Management of patients with liver diseases on the waiting list for transplantation: a major impact to the success of liver transplantation. BMC Med. 2018;16(1):113.

MELD/MELD Na – highly predictive of mortality while on wait list

MELD-Na Score	90-day mortality
<17	<2%
17-20	3-4%
21-22	7-10%
23-26	14-15%
27-31	27-32%
≥32	65-66%

Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008 Sep 4;359(10):1018-26.

What to do with high MELD/MELD-Na?

- Highly debatable
- High mortality risk post LT
- Are we wasting precious supply ?

- Is it futile?
- Increasingly admitted to ICU for organ support
- Survival benefit high in acute severe alc hepatitis & ACLF

<u>MELD/MELD Na > 35 :</u>

High risk of transplant mortality

Over indication for LT

Post operative morbidity and ICU stay significantly high

For intermediate MELD/MELD Na

- Get the patient to best possible state pre transplant
- Treat Hep C cirrhotics
- Regular US screening with doppler for HCC
- Prevent UGIB with regular endoscopy
- Refractory ascites: TIPS/paracentesis
- Avoid Malnutrition
- Exercise

Frailty

- ***"Biological syndrome of decreased reserve and resistance to stressors due to cumulative decline across multiple physiological systems and causing vulnerability to adverse outcomes."***
- Prevalence in LT wait list 17-49%
- Reason for de-listing!
- Associated with:
    - Longer hospital stay
    - Increased hospitalization
    - High wait list mortality
- Liver frailty index: Hand grip strength, chair stand, balance
- **Combined with MELD/MELD Na – more predictive of 3/12 mortality in wait list**

Lai et al.   Page 14

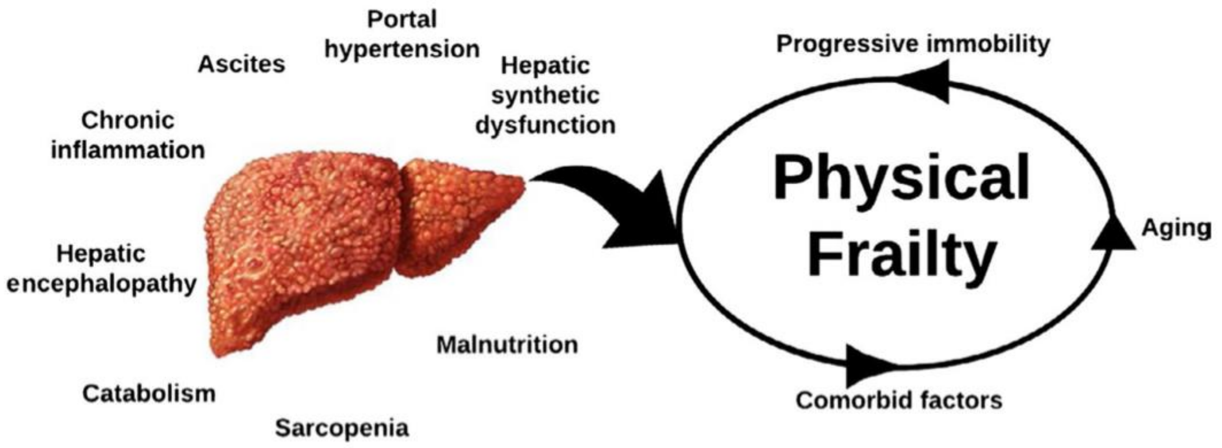


FIGURE 1.
Liver-related and non-liver-related factors that contribute to the development of physical frailty in patients with cirrhosis

Lai JC, et al. Frailty in liver transplantation: An expert opinion statement from the American Society of Transplantation Liver and Intestinal Community of Practice. Am J Transplant. 2019 Jul;19(7):1896-1906

How to manage those on waitlist for LT?

Risks
Infection
Bleeding
CVS events
HE
Hyponatraemia
Ascites
HCC
Poor Nutrition
Alcohol relapse
Psychological issues
Renal dysfunction

1. Infection

Prevalence : ~50%, 4x mortality rise

Increased surveillance for infection

Commonly : UTI / LRTI/ SBP

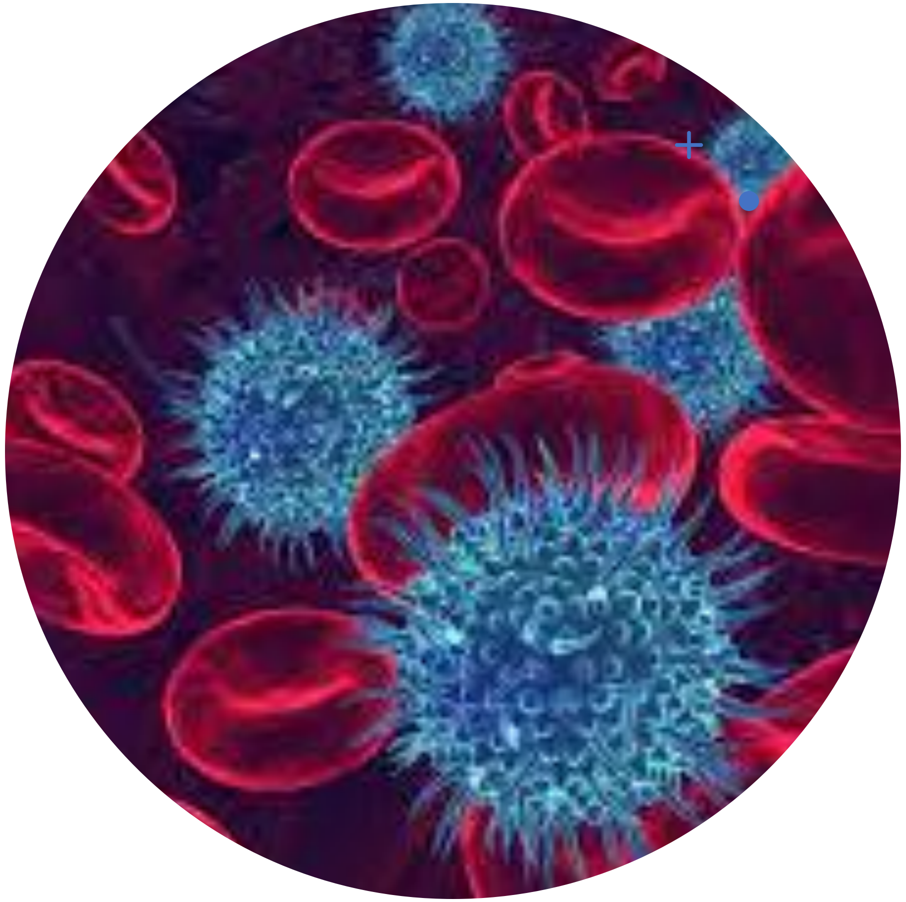
Can precipitate other complications : HRS/ HE

Vigilance for TB / COVID-19

Broad spectrum abx

Multiple cultures to send

Rising trend of MDR infections



lferink, L.J.M. et al . The impact of infections on delisting patients from the liver transplantation waiting list. Transpl Int. 2017; 30: 807-816

Spontaneous Bacterial Peritonitis

- Prevalence ~ 10-30%
- Mortality 30%
- AFFR + Cultures to send
- Commonly: Gram (-)= 65%,
  - gram + = 35%
- Repeat tap in 48hrs to assess cell count
- IV 3rd gen cephalosporin
- IV albumin infusion:
  - Day 1: 1.5g/kg & day 3: 1g/kg
  - Reduce risk of renal failure
  - Reduces mortality from 30% to 10%.
- Recurrence risk 70%
  - Need prophylaxis: Norfloxacin 400mg OD
  - Watch out for fungal /MDR infections

The European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. JHepatol (2018)

2. Bleeding

Risk of variceal bleeding 20–30%

Regular variceal screening

Variceal ligation – repeated till oesophageal varices disappear

Cyanoacrylate glue – gastric varices

Beta blocker prophylaxis

Can precipitate HE/ SBP

Acute bleeding:

IV terlipressin /

IV octreotide with IV PPI and Abx

Optimize Hb

Check INR and correct coagulopathy

Cardenas, Andres & Ginès, Pere. (2011). Management of patients with cirrhosis awaiting liver transplantation. Gut. 60. 412-21.

3. Renal dysfunction

AKI in cirrhosis

- **Rise in S. Cr by ≥0.3mg/dl in 48hrs or S.Cr ≥ 50% from baseline within 7/7**
  - Cr tend to be low in CLCD – low muscle mass/ protein malnutrition, increased Cr tubular secretion
  - UOP not used – diuretics / collection errors
- Treat underlying cause:
  - Pre renal/ renal/post renal
  - Commonest: Pre renal– Hypovolaemia : diuretics / bleeding/sepsis
- Omit Diuretics/beta blockers
- Optimize vol status (Crystalloid or blood)
- Watch out for HRS

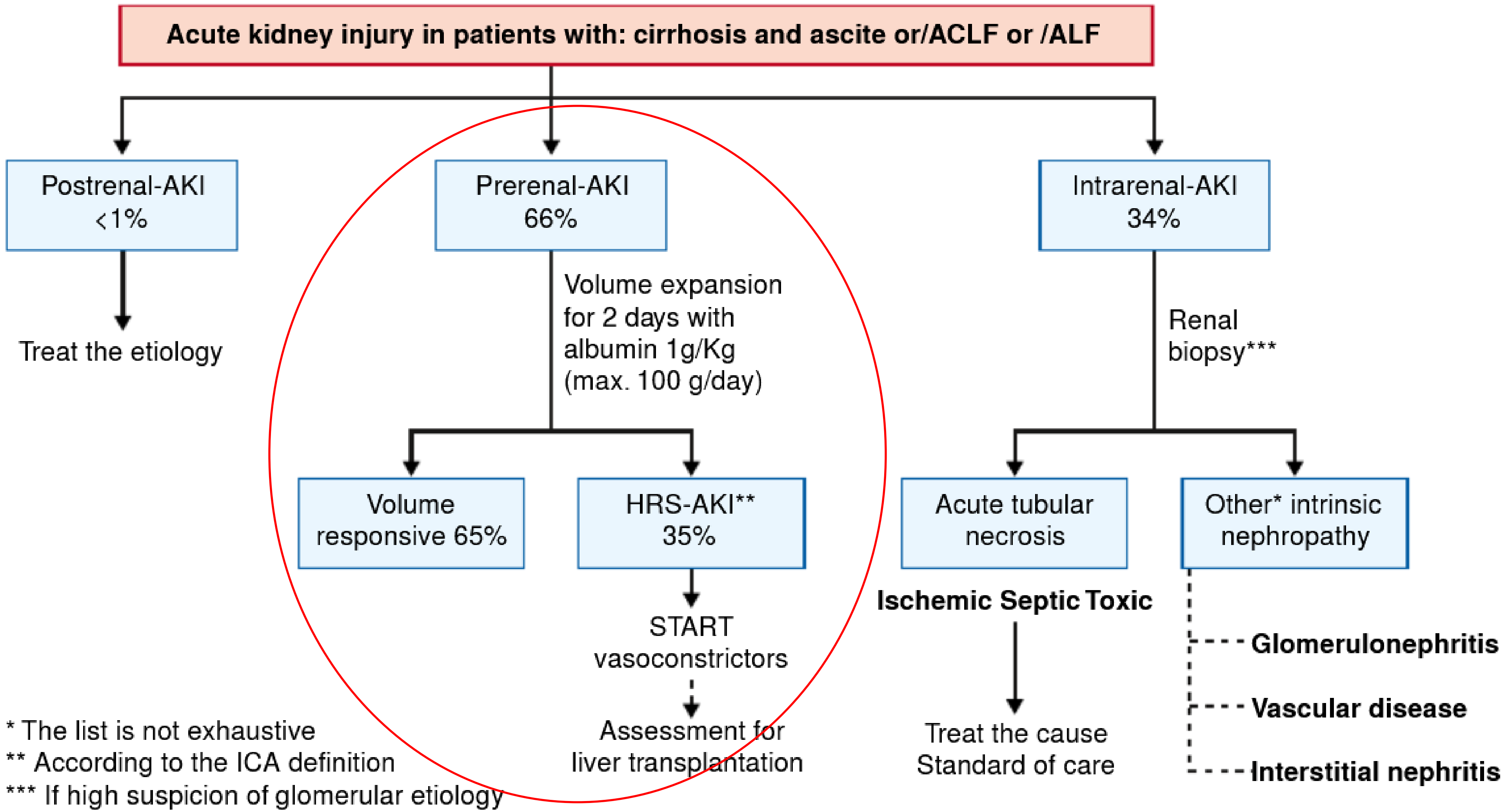


FIGURE 1 Diagnostic approach of acute kidney injury in patients with cirrhosis. ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ALF, acute liver failure

Sanchez LO, Francoz C. Global strategy for the diagnosis and management of acute kidney injury in patients with liver cirrhosis. United European Gastroenterol J. 2021 Mar;9(2):220-228

HRS-AKI

NO full or partial response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with Albumin 1g/kg

No structural kidney injury / shock/ nephrotoxins

MAP goal 60-65mmHg

Treat with IV albumin

20-40g/day

+

Vasoactive drugs

(NA or Terlipressin)

Ascites: drain with albumin cover & Abx for sepsis

Renal replacement therapy if non respondent

Consider LT

Sanchez LO, Francoz C. Global strategy for the diagnosis and management of acute kidney injury in patients with liver cirrhosis. United European Gastroenterol J. 2021 Mar;9(2):220-228

4. Hepatic encephalopathy

- Prevalence: 30-40%,
- High mortality & hospitalization

Table 3. West Haven Criteria Grading System of Hepatic Encephalopathy

Grade	*Description*
1	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
2	Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior
3	Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
4	Coma (unresponsive to verbal or noxious stimuli)

Information from reference 17.

Treat underlying cause

- Infection
- Bleeding
- Constipation
- Diuretic overdose
- Electrolyte imbalance
- Alcohol binge
- Malnutrition
- TIPS

Hepatic Encephalopathy

- Bowel opening 2-3x with laxatives
  - Lactulose / enemas
- Prophylaxis with Rifaximin 550mg BD
  - Better safety profile
- IV Albumin
  - As low albumin can further facilitate HE
- IV LOLA (L-Ornithine L-Aspartate)
  - Stimulate urea cycle - remove NH_3
- No protein restriction

The European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. JHepatol (2018)

5. Ascites

5% to 10% of compensated CLCD /yr

2yr mortality 40-50%

Independent predictors for mortality

- Hyponatraemia
- Low arterial pressure
- GFR
- Low renal Na+ excretion

Table 2. Grading of ascites.

Grade 1.	Mild ascites: it is only detectable by ultrasound examination
Grade 2.	Moderate ascites: it is manifest by moderate symmetrical distension of abdomen
Grade 3.	Large or gross ascites: it provokes marked abdominal distension

The European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. JHepatol (2018)

Grade 2 ascites :

Diuretics

- Initially Spironolactone
- Add frusemide if poor response
- max wt loss =

0.5kg/day (if no oedema)

1 kg/day (with oedema)

- Low salt intake : 2g/day

AFFR + therapeutic drainage

(Have high suspicion for TB/Malignancy)

If SBP – treat with broad spectrum Abx

Prophylaxis

IV albumin:

reduce mortality,

reduce renal impairment

Grade 3 ascites:

Large volume paracentesis with albumin cover

Refractory ascites

(6/12 survival ~50%)

: repeated LVP + albumin

Or

TIPS

6. Electrolyte imbalances: Hyponatraemia

Hyponatraemia associated with HRS / refractory ascites

Mortality significantly higher in cirrhotics with hyponatremia (26%)

Resolution of Na is an independent predictor of 30day survival

5% risk of death increase for each decrease of 1 Na+ unit within 125 to 140 mEq/l.

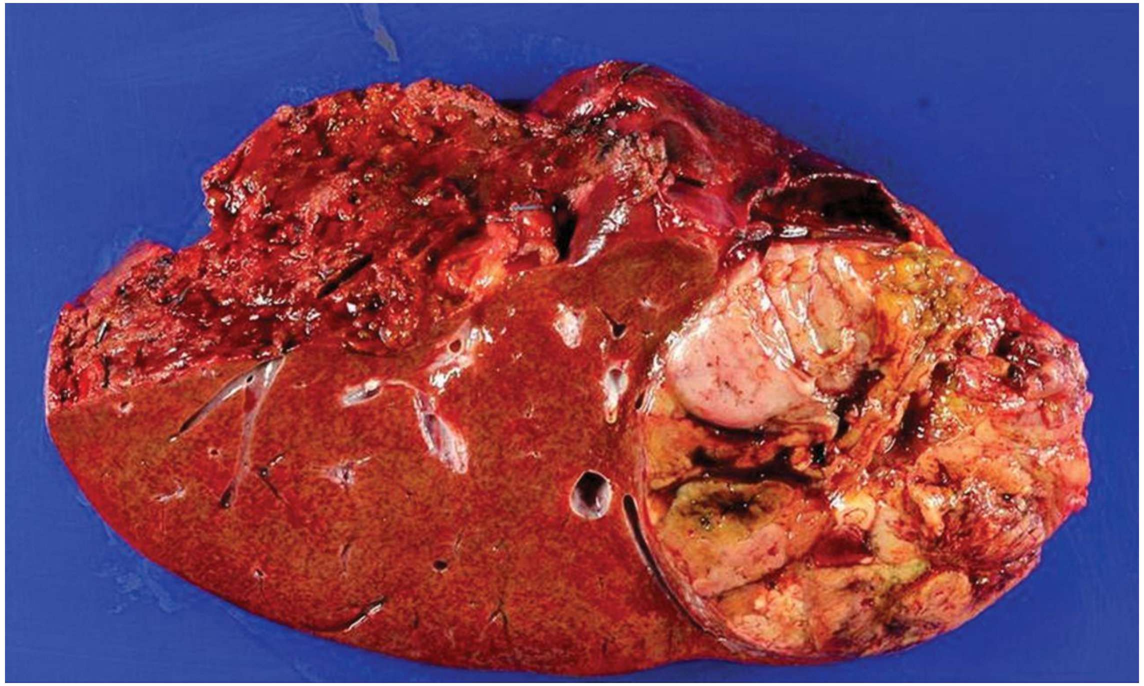
Mx
Keep S. Na >125
At the borderline = impending HRS !
Withhold diuretics, correct hypo K+
Fluid restriction <1.5L/day
IV albumin
IV Replace Na if clinical features / < 120

Angeli P, Wong F, Watson H, Ginès P, CAPPS Investigators. Hyponatremia in cirrhosis: Results of a patient population survey. Hepatology. 2006 Dec; 44(6):1535-42.

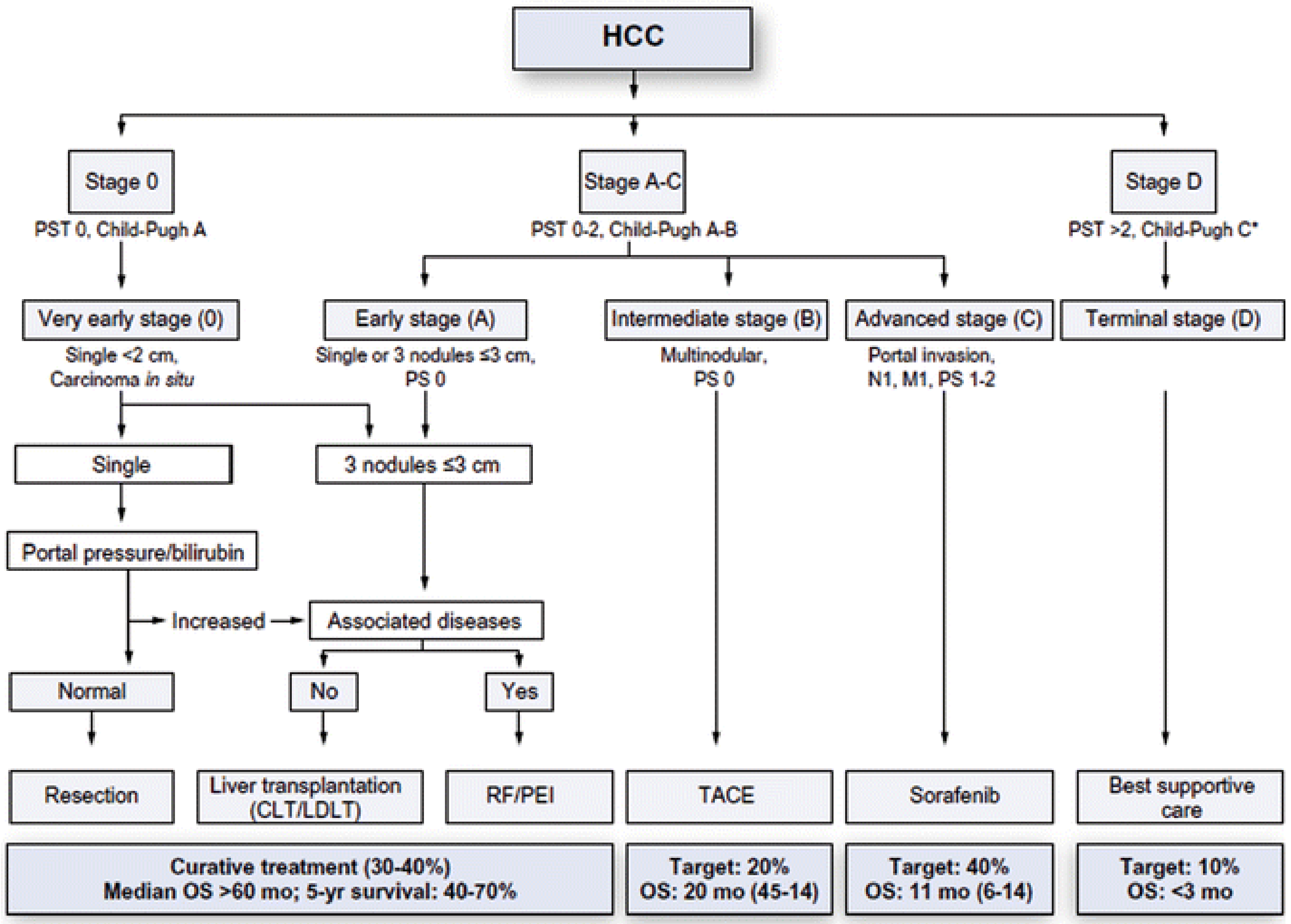
Attar B. Approach to Hyponatraemia in Cirrhosis. Clin Liver Dis. 2019; 13(4): 98–101

7.Hepatocellular carcinoma

- Majority well compensated with low MELD
- Gain points with waiting time
- Treat to downstage tumour (BCLC criteria)
  - Place within transplant criteria
  - Reduce progression
- 3 poor prognostic factors:
  - Regular increasing AFP
  - AFP > 1000
  - Invasion of Portal vein



BCLC criteria for treating HCC



Box 1
Selection criteria for liver transplantation

UNOS

- Stage T1 (1 tumor <2 cm) and stage T2 (1 tumor 2–5 cm or 2–3 tumors $\leq$3 cm)

Milan criteria

- Most common eligibility criteria for LT among patients with HCC
- Single lesion $\leq$5 cm or 2 to 3 lesions each $\leq$3 cm

Expanded criteria

- UCSF: a single HCC $\leq$6.5 cm or $\leq$3 tumors, with the largest $\leq$4.5 cm and a total tumor burden $\leq$8 cm[21]
- Up to 7: HCC with 7 as the sum of the size of the largest tumor (in cm) and the number of tumors[22]

Unzueta A, Cabrera R. Treatment Options in Patients Awaiting Liver Transplantation with Hepatocellular Carcinoma and Cholangiocarcinoma. Clinics in Liver Disease. 2017; 21(2): 231-251

8. Poor nutrition

95% OF CTP-C Cirrhotics are malnourished

<u>Sarcopenia</u> = *generalized and progressive loss of skeletal muscle mass, strength, and function*

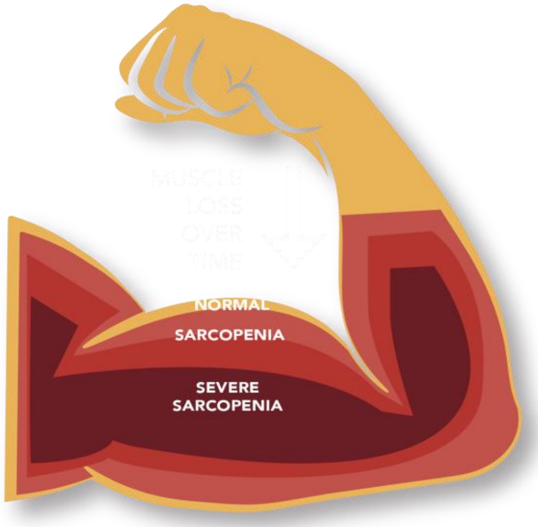
Seen in 70% in decompensated CLCD

Low calorie diets harmful

Quantify muscle mass = CT

Combine resistance & endurance exercise for benefit

HRT with growth hormone/ testosterone



Burra P and Zanetto A. Mistakes in liver transplantation and how to avoid them. UEG Education 2020; 2020: 1–6

- **<u>Sarcopenic obesity</u>**

Higher pre-LT mortality

Treat even if low MELD

- **<u>Obesity</u>** is on the rise = NASH/ metabolic syndrome

Fat mass	High	Sarcopenic obesity	Obesity
	Low	Sarcopenia	Healthy
		Low	High
		Muscle mass	

Nutritional interventions

- Proper counselling & dietary assessment
- Nutrition supplements
- Multivitamins, minerals, calcium, zinc and magnesium
- Role of BCAA
  - Significant improvement in QOL & prognosis
  - Reduced incidence of complications - liver failure, esophageal varices rupture, HCC, and death

9. Alcohol relapse

- **15-20% on wait list !**
- Monitor for relapse
- Refer to addiction services
- Counselling
- Smoking cessation
- Prognostic score = SALT criteria > 5 = not for LT

Criteria	Points
>10 drinks/ day at initial hospitalization	4
multiple prior rehabilitation attempts	4
prior alcohol-related legal issues	2
prior illicit substance abuse	1

Lee BP, et al. Predicting Low Risk for Sustained Alcohol Use After Early Liver Transplant for Acute Alcoholic Hepatitis: The Sustained Alcohol Use Post-Liver Transplant Score. Hepatology. 2019 Apr;69(4):1477-1487.

10. Psychological issues

- Surgery /post surgical survival fears
- Concurrent alcohol/ drug abuse
  - High rates of depression/anxiety
  - Reduces Pre-LT survival
  - Reduced QOL
  - Poor adaptive coping
  - Reduced functionality
- Mx
  - Educate family
  - Reassurance
  - Psychotherapy
  - Spiritual support

Golfieri L, et al. Impact of psychosocial status on liver transplant process. Annals of Hepatology. 2019;18 (6): 804-809

11. Cardiovascular events

- High resting CO
- Low SVR

In ESLD

- Cirrhotic cardiomyopathy in 40-50%
- Incidence of CAD ~ 27% in ESLD
- CAD+ increases 30day perioperative outcome
- High risk of CVS instability during surgery
- Other co-morbidities / anaemia can complicate further

Hogan BJ, Gonsalkorala E, Heneghan MA. Evaluation of coronary artery disease in potential liver transplant recipients. Liver Transpl. 2017 Mar;23(3):386-395.

Further optimizing the patient:

MANAGE CO-MORBIDITIES

ELECTIVE SURGERIES

Managing Co-morbidities

1. Obesity

increased risk of perioperative complications

reduced long-term survival

BMI >40 = Class 3 obesity relative CI to LT

2. DM/Dyslipidaemia/HTN/ Metabolic syndrome

Prevalence in recepients: HTN (40–85%),

Dyslipidaemia (40–70%),

DM (10–65%)

Cumulative risk of CVS event ~ 25% at 10 yrs post-LT

Managed as per general population

- Diet Exercise
- ACEI, Statin, Insulin/OHG

Require routine follow up

Managing Co-morbidities

3. **Viral hepatitis**

Sustained viral response : undetectable viral replication at 6 mths post treatment

Need regular follow up

De-listing if improve

4. Remain up-to-date with immunization

Hepatitis A & B

Pneumococcal

Seasonal Influenzae

<u>COVID-19 vaccine!</u>

5. Advice lifestyle modification & exercise

COVID-19 & those on the wait list for LT

- According to COVID-Hep.net

In CLCD with COVID 19

High risk of

  - hepatic decompensation
  - increased mortality

Other risk factors for death: advancing age and alcohol-related liver disease.

- Mortality ~ 70% in CTP-C
- **Overall mortality in Cirrhotics = 38%**
- **NO specific evidence to contradict the safety and generation of protective immunity by vaccines against COVID-19 in CLCD**

Marjot, T et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. Journal of Hepatology. 2021: 74(3): 567 - 577

Table 3. Summary of data for COVID-19 vaccines approved* to date (as of February 2021).

Vaccine	Phase III data	Special features	Ref
BNT162b2 (Tozinameran; Comirnaty) (BioNTech and Pfizer) RNA (embedded in lipid nano-particles) encodes a variant of the SARS-CoV-2 spike protein	N = 43,548 (randomised 1:1 vaccine *vs.* placebo) Efficacy 95% (9 vaccinated *vs.* 169 controls with COVID-19) 10 cases of severe COVID-19; 9 in the placebo group Safety: Injection site reactions and systemic AEs (headache, fever, fatigue) most mild to moderate. SAE rates were below 4%.	2 doses (30 µg) 21 days apart Storage at a temperature of -90 to -60°C for 6 months, storage at 2 to 8°C for up to 5 days and for up to 2 hours at room temperature (up to 30°C).	42
mRNA-1273 (Moderna) RNA (embedded in lipid nano-particles) encodes a variant of the SARS-CoV-2 spike protein	N = 30,420 (randomised 1:1 vaccine *vs.* placebo) Efficacy 94.1% (11 vaccinated *vs.* 185 controls with COVID-19) 30 cases of severe COVID-19 only in the placebo group Safety: Injection site reactions and systemic AEs (headache, fever, fatigue) most mild to moderate. SAE rates were low after the first dose and increased to around 16% after the second dose.	2 doses (100 µg) 28 days apart Storage at a temperature of -25 to -15 °C for 7 months, storage at 2 to 8°C for up to 30 days and at 8–25°C for up to 12 hours, 6 hours after first dose was taken.	43
ChAdOx1 nCoV-19 (AZD122) (AstraZenenca and University of Ox-ford) replication-deficient chim-panzee adenovirus vector, containing the full-length codon-optimised cod-ing sequence of SARS-CoV-2 spike protein.	Interim analysis (N = 11,636 from Brazil, South Africa, UK) Vaccine *vs.* MenACWY Efficacy 70.4% (30 [0.5%] of 5,807 vaccine recipients *vs.* 101 [1.7%] of 5,829 controls with COVID-19) Efficacy with 2 standard doses 62.1% Efficacy low dose/standard dose 90.0% Efficacy after 1 standard dose 64.1% Safety: 175 SAEs in 168 participants, 84 SAEs in the vaccine group and 91 in the control group.	2 doses. A second dose could be given between 4 and 12 weeks after the first dose. Detailed storage information pending but expected to be less complex (stable at 2–8°C). The number of patients aged ≥70 years was low (3.8%).	44

AE, adverse event; SAE, serious adverse event (grade 3); MenACWY, meningococcal group A, C, W, and Y conjugate vaccine. *by EMA or FDA (AZD122 so far only authorised in the UK, EMA/FDA approval was pending at submission of the manuscript).

Cornberg M, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. J Hepatol. 2021 Apr;74(4):944-951.

Elective surgery

10% of CLCD pts will undergo surgery during their last year of life

Commonly seen elective surgeries:

Umbilical hernia repair

- Incidence 20%
- Correlated with previous ascites, poor nutritional status
- Can be done at the time of LT

Cholecystectomy

- High prevalence, rarely symptomatic
- Can be done safely
- High risk of conversion & bleeding complications

Risk of Mortality after surgery

CTP class	Elective	Emergency
CTP A	10%	22%
CTP B	30%	38%
CTP C	82%	100%

Mansour A, Watson W, Shayani V, et al. Abdominal operations in patients with cirrhosis: Still a major surgical challenge.Surgery1997; 122: 730–735

Monitoring in clinics : core concepts

- Avoid decompensation : Complications of Cirrhosis
- HCC surveillance
- Sepsis
- UGI bleeding
- Nutrition

Conclusions

- Listing of patients for liver transplantation is only the first step in a long and difficult journey
- While waiting, patients can experience many complications of CLCD
- Management of the complications allows to optimize chances of patients reaching a desirable outcome
- Important to prevent, recognize and institute early treatment of complications

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15. Cornberg M, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. J Hepatol. 2021 Apr;74(4):944-951.

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Questions?