What is challenging in the management of chronic liver diseases in 2020?

# Lessons learned from COVID-19 in hepatology

**Covid-19 and Liver Transplantation** 



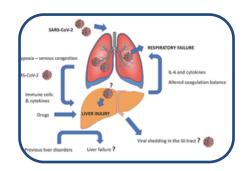
## **Disclosures**

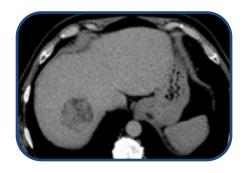
#### Marina Berenguer

- Abbvie: speaker, advisory board
- Gilead: Grant
- Novartis: speaker
- Astellas: speaker
- Intercept: advisory board. Speaker
- Orphalan: advisory board
- Alexion: advisory board
- Deep genomics: advisory board

## **Agenda**





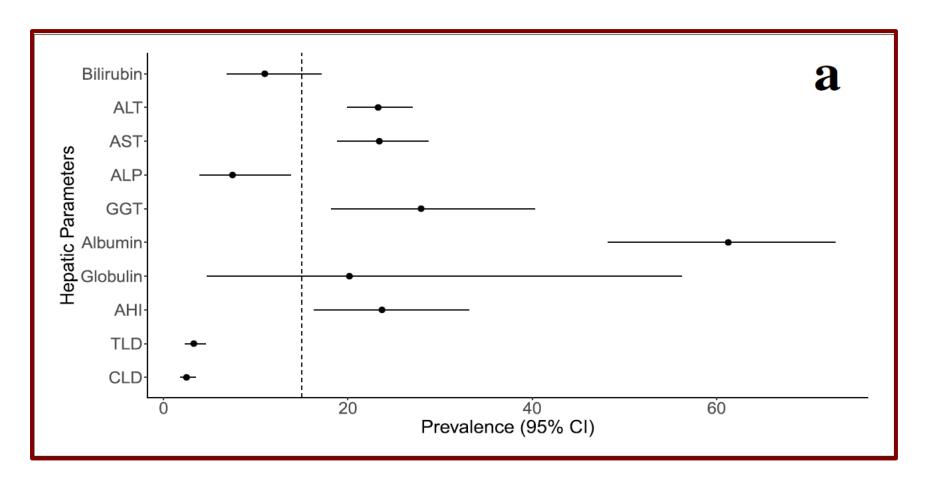


Covid and underlying CLD (including HCC)



Covid and the LT patient

## Liver enzymes abnormalities



14%-53% of hospitalized patients (rate vary depending on geographic location, disease severity, timing of measurement, prevalence of underlying CLD...)

## Liver injury and covid-19 disease severity

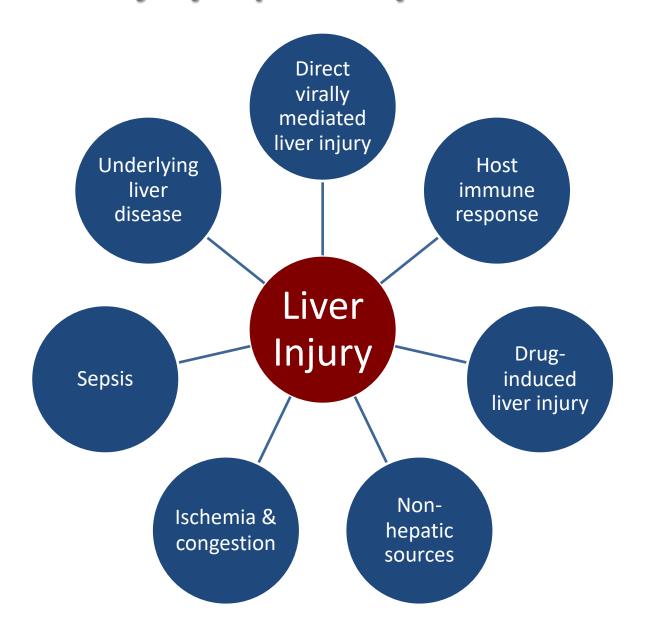
tudy name	Subgroup within study						Eve	ent rate and 95%	<u>CI</u>	
		Event rate	Lower limit	Upper limit	Total					
uang C, China	Non-severe	0.250	0.124	0.439	7/28	1	1	<b>⊢</b> ⊢	<b>-</b> ∣	
ang Z, China	Non-severe	0.310	0.202	0.443	17 / 55			-	<b>-</b>	
hi H, China	Non-severe	0.270	0.106	0.536	4/15			-	•──	
YK, China	Non-severe	0.500	0.273	0.727	8/16				<del></del>	
heng F, China	Non-severe	0.076	0.041	0.136	10 / 131			-		
an S, China	Non-severe	0.160	0.099	0.248	15 / 95			-	.	
u X, China	Non-severe	0.083	0.035	0.185	5/60			-		
uan WJ, China	Non-severe	0.182	0.153	0.214	112 / 615			•		
X, China	Non-severe	0.233	0.187	0.287	64 / 275			_   •	•	
eterogeneity: Tau <sup>2</sup> =0 st of overall effect:	3.18; Q=32.65; df=8; f=75.5; p<0.00 Z>7.62.p<0.001	0.199	0.148	0.263	242 / 1290			•	.	
luang C, China	Severe	0.620	0.347	0.833	8/13				-	_
Vang Z, China	Severe	0.430	0.208	0.685	6/14			•	━━	
hi H, China	Severe	0.590	0.468	0.702	39 / 66				+=-	
heng F, China	Severe	0.400	0.243	0.581	12 / 30				━	
Van S, China	Severe	0.375	0.240	0.532	15 / 40				━	
u X, China	Severe	0.180	0.119	0.263	20 / 111				•	
then N, China	Severe	0.434	0.340	0.533	43 / 99				-■+	
Buan WJ, China	Severe	0.394	0.317	0.477	56 / 142				-	
i X, China	Severe	0.434	0.376	0.494	115 / 265				-	
		0.411	0.331	0.405	314 / 780	ı	ı	- 1	_	

Forest plot of studies reporting the incidence of elevated liver chemistries in severely infected and non-severely COVID-19 patients

Study name	SI	tatistics fo	or each st	tudy	Even	ts / Total	(
	Odds ratio	Lower limit	Upper limit	p-Value	Severe	Non-severe	
luang C, China	4.895	1.196	20.033	0.027	8 / 13	7 / 28	
Shi H, China	3.891	1.125	13.457	0.032	39 / 66	4 / 15	
Vang Z, China	1.679	0.504	5.589	0.398	6 / 14	17 / 55	
heng F, China	8.105	3.056	21.494	0.000	12 / 30	10 / 131	
Van S, China	3.150	1.356	7.318	0.008	15 / 40	15 / 95	
i YK, China	1.247	0.242	6.428	0.792	5/9	8 / 16	
i X, China	2.524	1.743	3.656	0.000	115 / 265	64 / 275	
u X, China	2.425	0.860	6.842	0.094	20 / 111	5 / 60	
Guan WJ, China	2.922	1.971	4.333	0.000	56 / 142	112 / 615	
				0.000	276 / 690	242 / 1290	

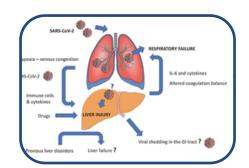
Forest plot showing the odds ratio of elevated liver chemistries at initial presentation in severe vs. non-severe COVID-19

## Liver Injury is probably multifactorial



## **Agenda**







Covid and underlying CLD (including HCC)



## **Chronic liver disease and covid 19**

- 1) Rate of patients with CLD in covid-19 cohorts:
- 1-11%
- In the largest cohorts, less tan 1%

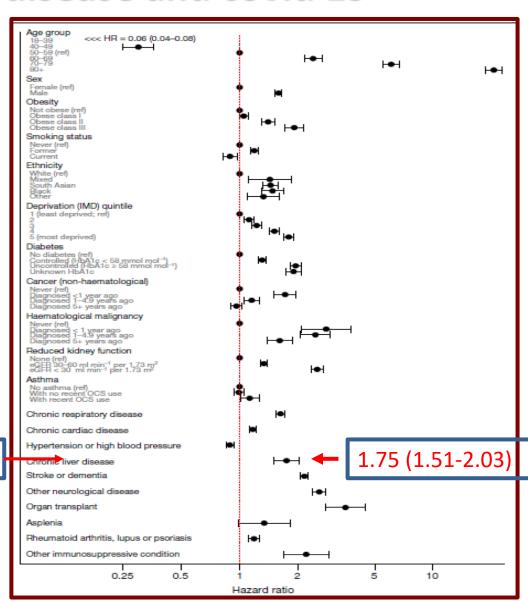


CLD not over-represented in covid-19 cohorts

2- May be associated with worse outcome (increased hospitalization and death)

**Chronic Liver Disease** 

17,278,392 adults pseudoanonymously linked to 10,926 covid-19 deaths



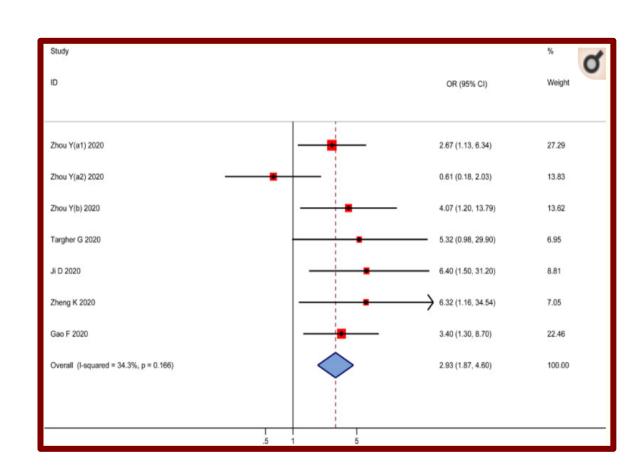
# Chronic liver disease and outcome following covid 19 infection

	Befo	ore propensity matching		After propensity matching			
	COVID-19 with liver disease (n = 250)	COVID-19 without liver disease (n = 2530)	RR, RD, or P	COVID-19 with liver disease (n = 250)	COVID-19 without liver disease (n = 250)	RR, RD, or P value	
Outcomes							
Mortality, %, (n/total)	12.0 (30/250)	4.3 (110/2530)	RR: 2.8 (1.9,	12.0 (30/250)	4.0 (10/250)	RR: 3.0 (1.5,	
			4.0)			6.0)	
			RD: 7.7%			RD: 8.0%	
			(3.5%, 11.75%)			(3.3%, 12.7%)	
			<i>P</i> < .001			P = .001	
Hospitalization rate	52.0 (130/250)	30.0 (760/2530)	RR: 1.7 (1.2,	48.0 (120/250)	36.0 (90/250)	RR: 1.3 (1.1,	
			2.0)			1.6)	
			RD: 22.0%			RD: 12.0%	
			(15.5%, 28.4%)			(3.4%, 20.6%)	
			P < .001			P = .006	

2,780 covid-19 patients in the US 150 (9%) with pre-existing liver disease (42% NAFLD) 50 (1.8%) with cirrhosis

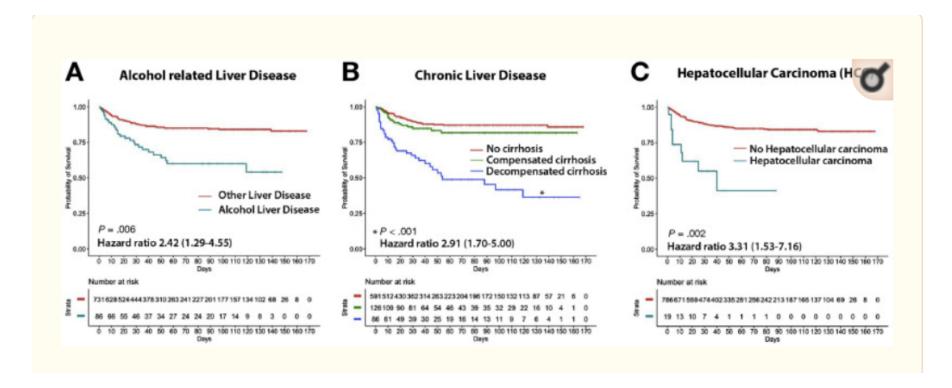
# Metabolic associated fatty liver disease increases the severity of covid-19

- \* Covid-19 outcomes associated with DM, AHT, CVD, & obesity
- \* US steatosis & indirect markers of fatty liver:
- Are common in cohorts with covid-19
- Have been associated with disease severity



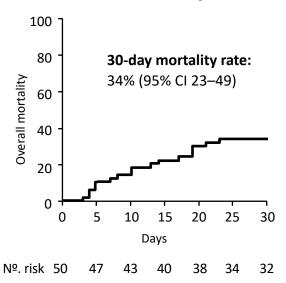
# Other predictors of outcome in patients with underlying cronic liver disease

867 patients from 21 centers across the US with CLD with COVID-19



## Is Severe Liver Disease or Cirrhosis Associated With Worse COVID-19 Outcomes?

#### **Cumulative Probability of Overall Mortality**



### Cirrhotics with COVID-19 vs cirrhotics with bacterial infection:

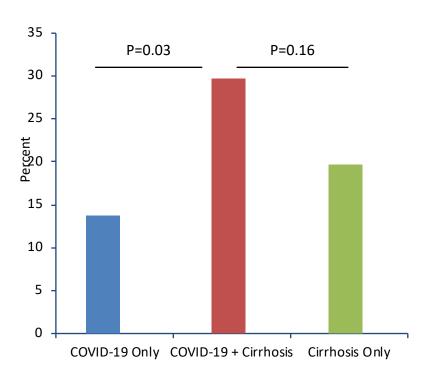
34% (95% CI 23–49) vs 17% (95% CI 8–32), P=0.03

#### Cirrhotics with COVID-19 vs noncirrhotics with COVID-19:

34% (95% CI 23–49) vs 18% (95% CI 15–22), P=0.035

#### Mortality comparison between groups

Mortality (in-hospital mortality and hospice) comparison between groups



International registry study

29 countries 130 centres over 105 days

# SARS-CoV-2 Infection in Patients with Chronic Liver Disease: Data From the COVID-Hep and SECURE-Cirrhosis Registries

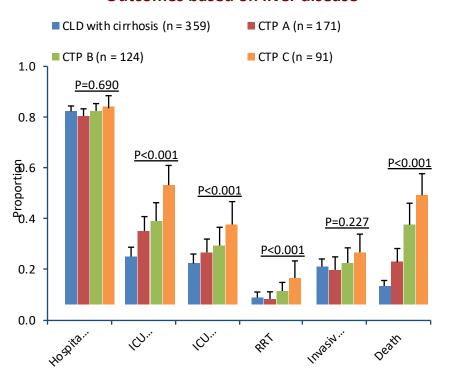
#### 1365 patients included

745 chronic liver disease

- · 359 without cirrhosis
- · 386 with cirrhosis

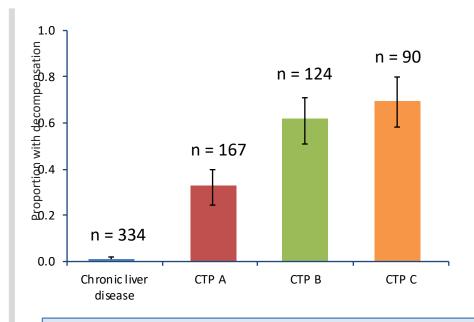
620 without liver disease

#### **Outcomes based on liver disease**



With each liver disease stage there is a stepwise increase in rates of major adverse outcomes including death

#### Acute hepatic decompensation following CoV-2 infection



**46%** of cirrhosis patients decompensate following SARS-CoV-2 infection

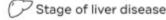
**22%** of those who decompensated had no respiratory symptoms at presentation

Main cause of death: respiratory (secondary: liver)

Major risk factors for mortality:

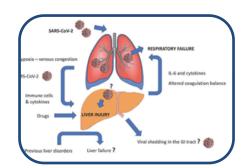


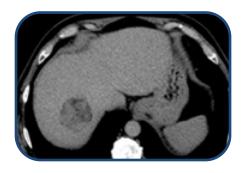
Alcohol related liver disease



## **Agenda**





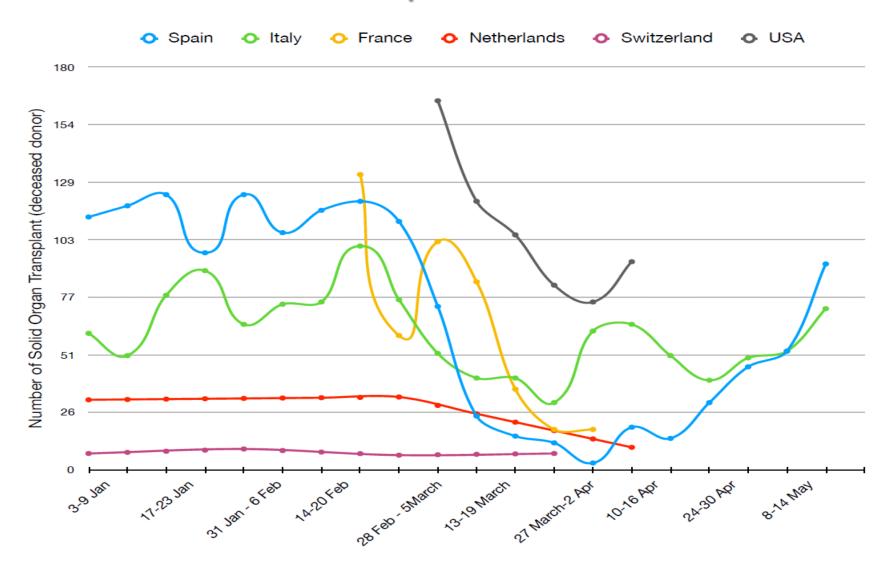


Covid and underlying CLD (including HCC)



Covid and the LT patient

# Trends of Solid Organ Transplantation (SOT) activity during COVID-19 outbreak in Europe and United States of America



Immunosuppression for hyperinflammation in COVID-

19: a double-edged sword?

Hyperinflammation

Perpetuation of illness

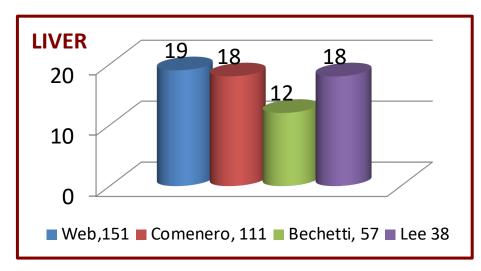
Possible beneficial effects of reducing inflammation should be carefully weighed up against the potential for deleterious impairment of antimicrobial immunity

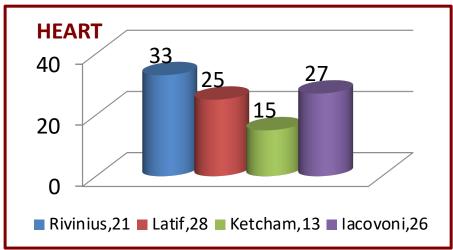
**Broad IS** 

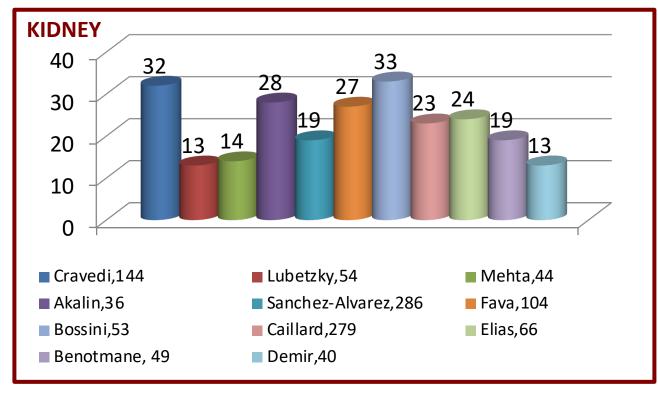
Delay virus clearance

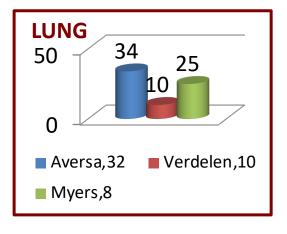
Inhibition of antiviral immunity

### **Mortality Rate**









Substantial
differences in
time from
transplantation
between
patients (--different
baseline IS
intensity)

Additional confounding variables (investigational agents, empirical antibiotic therapies, ICU admission protocols, changes in IS due to DDI, ...)

Insufficient data on clinical outcome variables (oxygen requirements, graft function...)

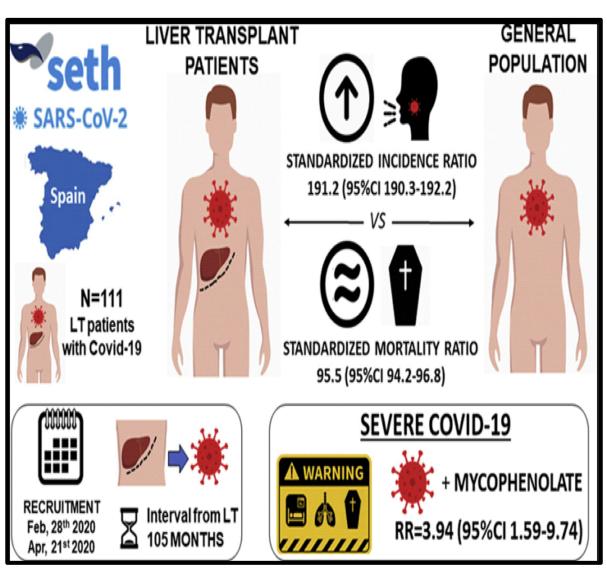
Large variation in transplant and clinical characteristics

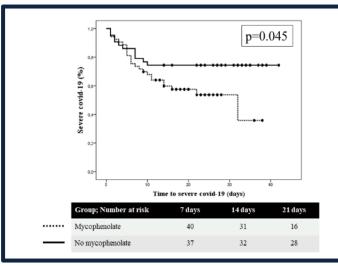
Large variation in SARS-CoV-2 and immunosuppressant management

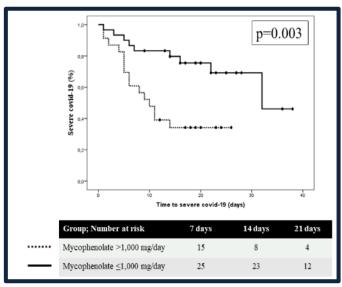
Difficult to assess
IS therapy,
appropriateness
of modifications,
and risk factors
for poor
outcomes

Very limited data (medication doses or target trough concentrations, risk factors for poor prognosis)

## **COVID-19** in LT patients







### Risk factor for poor outcome: IS? Metabolic factors?

	Long-term liver transplant recipient (>10 years, n=111)	Short-term liver transplant recipient (<2 years, n=40)	pvalue
Age older than 65 years	55 (50%)	12 (30%)	0.04
Overweight or obesity (body mass index > 25 kg/m²)	89 (80%)	24 (60%)	0-02
Diabetes	67 (60%)	9 (23%)	0.0001
Hyperlipidaemia	50 (45%)	7 (18%)	0.002
Arterial hypertension	111 (100%)	27 (68%)	0.0001
History of cardiovascular event	39 (35%)	2 (5%)	0.0015
Chronic kidney disease	44 (40%)	8 (20%)	0.03
Full immunosuppression*	11 (10%)	28 (70%)	0.0001
COVID-19-related deaths	3 (3%)	0	0.57

COVID-19–coronavirus disease 2019. \*Ciclosporin concentration more than 150 ng/mL or tacrolimus concentration more than 5 ng/mL.

Table: Characteristics of liver transplant recipients in Istituto Nazionale Tumori, Milan

Bhoori S et al. Lancet Gastroenterol Hepatol 2020

#### **ELITA/ELTR Registry**

Mortality was observed only in patients aged 60 years or older (16 [22%, 95% Cl 13–33] of 73 patients vs none [0%, 0–13] of 27 patients younger than 60 years),

Although not statistically significant, more patients who were transplanted at least 2 years previously died than did those who received their transplant within the past 2 years (15 [18%, 95% CI 11–28] of 82 patients vs one [5%, 0–24] of 21 patients;

www.thelancet.com/gastrohep

#### International registry (n=151) Webb GJ et al; Lancet G&H

- Age (OR 1.68/10yrs; 95%CI 1.02-2.80)
- Serum creat (OR 1.56/mg/dl; 1.-2.33)
- Non-liver cancer (OR 18.61; 1.94-178.98)

### Take home messages

During a pandemic, international collaboration using large-scale registries allows for rapid accumulation of data on well characterised cohorts of patients.

Increasing risk of ICU and death with each liver disease stage (CLD without cirrhosis, CTP-A, CTP-B, CTP-C)

Predominant cause of death is COVID-19 lung disease even in those with acute hepatic decompensation

New decompensation occurs in almost half of patients with cirrhosis, some of which will not have respiratory symptoms at presentation (high suspicion)

Independent risk factors for death in patients with CLD include age, CTP class and alcohol related liver disease

LT recipients are a vulnerable population at high risk of infection. Standardized mortality rates however are similar to those seen in the general population

Independent risk factors for death in LT patients include age and comorbidities.

Most Societies recommend maintaining the same IS therapy . Reduction (MMF) should only be considered under special circumstances .