Modulating immunosuppression in liver transplant patients with COVID-19

We read with great interest the COVID-LT study by C Becchetti *et al*,[1] which included 57 liver transplant (LT) patients from 12 European institutions who were diagnosed with coronavirus disease 2019 (COVID-19). Simultaneously, the Spanish Society of Liver Transplantation (SETH) has conducted a nationwide prospective study including 22 transplant institutions and 111 LT patients with COVID-19.[2] Since there were only nine overlapped cases, both cohorts add up to 159 LT patients and taken together their close analysis (table 1) may derive in practical conclusions.

The crude incidence of COVID-19 was increased in the SETH study as compared with the COVID-LT study (0.84% vs 0.48%), even with a shorter recruitment period. This could be explained because the SETH study was performed during the outbreak period in Spain, one of the toughest in Europe.[3] The SETH study allowed to calculate standardised incidence ratio (SIR) and found that LT patients may have doubled risk of acquiring COVID-19 within an epidemic scenario (SIR 191.2; 95% CI 190.3 to 192.2) as compared with age-matched and gender-matched general population.[2] Although LT patients could have been tested more frequently for COVID-19 given their lifelong clinical surveillance, this may have had limited influence in the SETH cohort as 93.7% of patients were symptomatic and there was no differential testing protocol for immunosuppressed or fragile patients according to the Spanish national authorities. Therefore, the increased SIR in LT patients claim for a stricter social distancing and to consider an earlier access to vaccination whenever available.

Clinical features and outcomes were much alike in both cohorts (table 1). The COVID-LT investigators hypothesised that the clinical course of COVID-19 in LT patients, despite increased comorbidities,[4] may not be more severe to that observed in non-liver transplant cohorts.[1] The results of the SETH study confirmed that mortality rates are actually lower in LT patients as compared with age-matched and gender-matched general population (standardised mortality ratio 95.5; 95% CI 94.2 to 96.8).[2] Noteworthy, no death was registered among LT patients younger than 50 years old in both cohorts.

The role of immunosuppression in COVID-19 could not be explored in depth by the COVID-LT investigators as the primary endpoint (ie, death) only occurred in seven patients. The SETH study used severe COVID-19 as a composite main endpoint, which comprised mechanical ventilation, admission to intensive care unit and/or death. Although death alone may be considered a harder outcome, severe COVID-19 may better capture the most severe forms of the disease and it was used in the original report of COVID-19 in China.[5] This composite endpoint allowed to analyse independent predictors of worse outcomes, including immunosuppression. Both cohorts showed that complete discontinuation of immunosuppression after COVID-19 diagnosis had no benefit. Regarding calcineurin inhibitors, in vitro studies have shown antiviral properties against coronaviruses.[6 7] In the COVID-LT study, the continuation on calcineurin inhibitor therapy after COVID-19 diagnosis was increased among survivors (64% vs 42.8%).[1] In the SETH study, baseline immunosuppression containing tacrolimus had a trend towards reduced risk of severe COVID-19 in the univariate analysis (relative risk (RR)=0.54; p=0.08). More importantly the SETH study showed that baseline immunosuppression containing mycophenolate was an independent predictor of severe COVID-19 (RR=3.94; p=0.003), particularly at doses higher than 1000 mg/day. Complete withdrawal

Table 1 Clinical characteristics and outcomes of LT patients included in the European COVID-LT cohort and in the nationwide study from the Spanish Society of Liver Transplantation (SETH)

	COVID-LT cohort[1]	SETH cohort[2]
	(n=57)	(n=111)
Recruitment period	10th March to 10th May (60 days)	28th February to 7th April (37 days)
Crude incidence during the recruitment period	0.48%	0.84%
Age	65 (IQR 57 to 70)	66 (IQR 61 to 73)
Gender (male)	70% (40)	71.2% (79)
Arterial hypertension	56% (32)	57.7% (64)
Diabetes	37% (21)	47.7% (53)
Cardiovascular disease	37% (21)	19.8% (22)
Respiratory disease	23% (13)	11.7% (13)
Diagnosis of COVID-19	Confirmed by a real-time reverse transcriptase PCR assay	Confirmed by a real-time reverse transcriptase PCR assay
Interval from liver transplantation <12 months	37% (21)	13.5% (15)
Symptoms at presentation		
Fever	79% (44)	74.8% (83)
Cough	55% (31)	70.3% (78)
Dyspnoea	46% (26)	41.4% (46)
Diarrhoea	28% (16)	34.2% (38)
Baseline immunosuppression (drugs)		
Calcineurin inhibitors	87.7% (50)	64.9% (72)
mTOR inhibitors	12.3% (7)	20.7% (23)
Mycophenolate	43.8% (25)	51.4% (57)
Changes in immunosuppression		
Unchanged	49.1% (28)	34.2% (38)
Reduction	22.8% (13)	52.3% (58)
Complete withdrawal	28.1% (16)	13.5% (15)
Follow-up for the last included patient	None	15 days
Hospital admission	72% (41)	86.5% (96)
Admission in intensive care unit	10% (4)	10.8% (12)
Case-fatality rate	12% (7)	14.4% (16)
Mortality rates*	Not reported	18% (20)
Predictors of worse outcomes (univariately)	Dyspnoea at presentation, lymphopenia, increased platelet counts, history of cancer, HCC prior to LT, active cancer.	Dyspnoea at presentation, lymphopenia, older age, Charlson comorbidity index, PaFiO2, radiological abnormalities and mycophenolate containing immunosuppression.
Predictors of worse outcomes (multivariately)	Not analysed	Dyspnoea at presentation, male gender, Charlson comorbidity index and mycophenolate-containing immunosuppression.

Continuous variables are expressed by median (IQR) while categorical variables are presented as percentages (absolute number).
*The COVID-LT only reported case-fatality rates. The SETH study reported mortality rates with a minimum follow-up of 15 days for the last included patient.
HCC, hepatocellular carcinoma; LT, liver transplant; mTOR, mammalian target of rapamycin.

of mycophenolate at COVID-19 diagnosis ameliorated the risk of severe COVID-19 (41.7% vs 69.2%; p=0.16).[2] The relationship between mycophenolate and severe COVID-19 could be explained by a synergic effect (viral and pharmacological) on depleting T-lymphocytes, with an increase in CD4+/CD8+ ratio, being both features strongly associated with worse outcomes.[8]

Taken together, the COVID-LT and the SETH cohorts suggest that chronic immunosuppression could exert a protective effect against the most severe forms of COVID-19 and complete withdrawal of immunosuppression may not be useful. Unlike calcineurin inhibitors, mycophenolate could be deleterious for COVID-19 successful resolution, thus providing a rationale to modulate immunosuppression in transplant patients with COVID-19. Further studies, randomised if possible, are required.

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