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Viewpoint

Graft injury and *re*-transplantation in liver transplant patients with COVID-19

Alexander Ng*

University College London, Gower Street, London, United Kingdom

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ABSTRACT

This article discusses the current scene of liver transplantation (LT) in light of the impact of COVID-19, with particular emphasis on the possibility of graft injury and re-transplantation in LT patients infected with SARS-CoV-2. A major concern is whether such patients experience a more severe form of disease which may lead to a higher risk of acute, irreversible liver injury. If this is serious, it may necessitate re-transplantation. This article aims to raise awareness in this relatively under-researched domain. More studies are required to evaluate this issue since it has strong implications in healthcare resource allocation and clinical decision-making. Several potential research directions are proposed, including the possibility of prolonging bridging therapy for non-urgent LT cases: patients with hepatocellular carcinoma; and whether hepatoprotective agents play a role in liver-sparing during SARS-CoV-2 infection. There is also substantial discussion of the relevance of lung injury in LT patients with COVID-19 since it is not uncommon regarding the high expression of ACE2 receptors in the lungs, and that lung injury remains the major cause of death in patients with chronic liver disease.

Liver transplantation has faced unprecedented challenges since the emergence of SARS-CoV-2 in Wuhan (China). In the US, numbers of living and deceased donor liver transplants (LTs) performed weekly decreased significantly from January to March 2020 [1]. Although numbers have risen roughly back to pre-pandemic levels in July and August 2020, the emergence of new COVID-19 variants such as the B.1.1.7 variant in the UK is expected to cause new disruptions to transplant activity.

Many questions regarding the association between COVID-19 and LT remain unresolved. One of them is graft injury induced by COVID-19 and the need for re-transplantation. Liver abnormality is identified as a possible sequela of COVID-19 infection. Biochemical abnormalities and liver injury are detected respectively in 27.3% (n = 227) and 3.9% (n = 32) of a Wuhan-based cohort of COVID-19 patients in general [2]. Most cases are attributable to severe COVID-19. A systematic review found that the pooled ORs of ALT elevation was 2.5, AST elevation was 3.4, and hyperbilirubinaemia was 1.7 amongst critically ill COVID-19 patients [3]. The presence of liver abnormalities in COVID-19 patients regardless of prior liver health makes us contemplate the extent and form of these changes in LT patients with COVID-19.

LT patients with COVID-19 can experience more severe disease than their non-transplant counterparts. According to Colmenero and colleagues [4], respectively 86.5% (n = 96) and 31.5% (n = 35) were hospitalised and met the criteria for severe COVID-19. The trends were corroborated by the results presented by Rabiee and colleagues [5], where 72.3 (n = 81) patients were hospitalised and 37.0% (n = 30) were admitted to the intensive care unit (ICU). Such studies, performed at the early stages of the pandemic, are prone to selection bias and lack comparator groups. However, according to two systematic reviews [6,7], ICU admission is higher in COVID-19 patients having received solid organ transplantation before. Higher disease severity is expected. By logic, there should be higher risk for LT patients to experience liver injury.

However, few data confirm the correlation, let alone establish the disease course. It is unknown whether liver abnormalities in transplant patients are transient or irreversible and, if the former, how long it takes for liver function parameters to normalise. Current evidence is optimistic. Colmenero and colleagues found that only 2.7% (n = 3) of LT patients with COVID-19 developed graft dysfunction [4]. None experienced graft loss. A US cohort [5] found 34.6% experienced

Abbreviations: ACE2, angiotensin-converting enzyme 2; ALT, alanine transaminase; AST, aspartate transaminase; BCLC, Barcelona Clinic Liver Cancer Staging; COVID-19, coronavirus disease 2019; DEB, drug-eluting beads; ICU, intensive care unit; JAK, Janus Kinus; LT, liver transplant; OR, odds ratio; TACE, transarterial chemoembolization; US, United States; UDCA, Ursodeoxycholic acid

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* Corresponding author.
E-mail address: a.ng.20@ucl.ac.uk

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liver injury, with significant increases in ALT (median, 23 vs 32 IU/L; $p<0.001$) and AST (median, 19 vs 41 IU/L; $p<0.001$) from baseline. The study also examined changes in liver function parameters in patients with clinical resolution of COVID-19. Such parameters were significantly decreased from peak levels (ALT: 40.3 vs 29.8; $p = 0.06$; AST: 44.9 vs 29.0; $p = 0.005$). However, they remained higher than baseline. It is unknown whether they would ever return to baseline and, if yes, when. A longer follow-up period is therefore required to tease out these changes. Moreover, the heterogeneity of COVID-19 severity in the cohort may have underestimated the impact of COVID-19 on liver function, especially in patients with severe disease. Nevertheless, this theory is not without caveat. Bangash and colleagues suggested that aminotransferase elevations may originate from myositis due to concurrent rises in myoglobin and creatinine kinase, instead of hepatic dysfunction [8]. Furthermore, innate immunity dysregulation and the presence of virally induced cytotoxic T cells are suggested to be more important explanations. The authors postulated that, as observed in other respiratory viruses, aminotransferase level elevations change according to respiratory disease course without hepatic viral replication. However, more recent academic opinion suggests there is higher risk that pathological changes within the livers of patients with severe COVID-19, including microvasculature thrombosis and hepatic steatosis are irreversible [9]. This leads to persistently elevated aminotransferase levels. More studies are required to confirm this correlation.

There are several remarks concerning observational studies on LT patients with COVID-19. Most studies are regional, carried out in the Western hemisphere, and feature small cohorts of limited diversity. Furthermore, transplant-to-infection times tend to be long. A more thorough assessment of the relationship between COVID-19 and the acute complications of LT, including hepatocellular injury secondary to graft rejection, is still wanting. There is also scarce literature on the prevalence and indication(s) of re-transplantation in LT patients with a history of COVID-19. Such studies are urgently required for better resource allocation and reducing pressure on healthcare facilities. *Re*-transplantation, for instance, poses pressure on organ supply, which is diminished with enhanced COVID-19 screening in donors [10].

Two potential research directions are proposed: (1) whether hepatoprotective agents play a potentially significant role in liver-sparing amidst COVID-19 in LT patients, and (2) whether bridging therapy for non-urgent, transplant-eligible patients with hepatocellular carcinoma can delay transplantation for longer periods of time. Ursodeoxycholic acid (UDCA), and N-acetylcysteine are shown to display hepatoprotective effects. According to a small randomised controlled trial [11], UDCA treatment effectively reduced liver enzymes in patients with abnormal baseline ALT levels at four weeks of follow-up. It was shown to regulate uraemic toxins, antioxidants, and the phenylalanine/tyrosine pathway. However, the data remain controversial [12]. Trials investigating the efficacy of UDCA in LT patients with COVID-19 to mitigate liver injury are recommended. Data on the efficacy of N-acetylcysteine are scarce and controversial. Early animal models indicate its amelioration of ischaemia/reperfusion injury, which is a key mechanism of liver injury in COVID-19, but a randomised controlled trial showed no improvement on graft function post-transplantation [13,14]. Clinical trials are needed to elucidate its effects on LT patients with COVID-19. In terms of bridging therapy, locoregional therapies are pivotal in reducing disease progression in transplant-eligible patients with hepatocellular carcinoma. Transarterial chemoembolisation (TACE) with drug-eluting beads (DEB) was found to elicit a complete response in over half (58%) of patients with BCLC-A hepatocellular carcinoma [15]. The response was maintained for seven months in over one-third of the cohort (31%). LT eligibility was maintained for a median of 19 months. Further studies could be executed to see if this delay could be lengthened by varying current regimens, thus improving healthcare resource allocation.

One should also not forget the importance of lung injury in LT patients with COVID-19. Efforts to treat liver injury should complement existing treatment paradigms to cope with lung injury, since COVID-19-related lung injury is the most common cause of mortality in COVID-19 patients with chronic liver disease. This is evidenced by the findings of Marjot, Moon and colleagues, where only 19% of all deceased patients died of liver-related complications [16]. Moreover, concomitant lung and liver injury amidst COVID-19 is not uncommon. According to Li and colleagues, the levels of expression of ACE2 receptors in the lungs and the liver are similar [17]. Fortunately, trials are underway to explore the efficacy of immunosuppressants in mitigating the harms resultant from lung injury. The TACROVID trial investigated the clinical utility of methylprednisolone pulses and tacrolimus in treating patients with severe COVID-19 pneumonia [18]. Of interest, the combination is found to be beneficial. Where tacrolimus-based immunosuppression does exhibit an advantage in mitigating lung injury, clinicians may be more inclined to continue immunosuppression by switching to, or maintaining the use of, tacrolimus. Moreover, the RuXoCoil trial aims to investigate the efficacy of ruxolitinib, a JAK1/2 inhibitor, in reducing the extent of lung injury experienced by patients with COVID-19 [19]. Trial results are pending, but the efforts of the trial investigators should be commended. Adding ruxolitinib, or other JAK inhibitors to the immunosuppression regimen in LT patients with COVID-19 is potentially beneficial due to further amelioration of pulmonary health during the disease course. Although JAK inhibitor-induced hyperlipidaemia may raise a concern in patients whose indication for LT is metabolic-associated fatty liver disease (with many patients suffering from predisposing patie metabolic syndrome) [20], this can be monitored regularly and controlled by polypharmacy such as statins, if necessary. More studies are also required to elucidate on the interactions between JAK inhibitors and existing immunosuppressants for LT patients safe for use in COVID-19.

Table 1
Anthropometric characteristics and outcomes in adult post-liver transplant patients with COVID-19 reported by major, large-scale studies.

	Colmenero et al. (2020) [4]	Rabiee et al. (2020) [5]	Webb et al. (2020) [21]	Dumortier et al. (2021) [22]	Becchetti et al. (2020) [23]
Origin	Spain	United States	United Kingdom, United States	France	Europe
Cohort Size	111	112	151	91	57
Age, years	65 (54–76)	61 (51–71)	60 (47–66)	64 (55–71)	65 (57–70)
Male	79 (71%)	61 (55%)	102 (68%)	64 (70%)	40 (70%)
Smoker	NR	44 (39%)	3 (2%)	13 (14%)	7 (12%)
White ethnicity	NR	31 (28%)	111 (74%)	NR	53 (93%)
Hospitalisation	96 (87%)	81 (72%)	124 (82%)	67 (74%)	41 (72%)
Median Duration of Hospital Stay, days	NR	7 (4–10)	11 (6–16)	NR	10 (7–22)
Mechanical Ventilation given	22 (20%)	26 (23%)	30 (20%)	33 (36%)	30 (54%)
Admission to ICU	12 (11%)	30 (27%)	43 (28%)	33 (36%)	4 (7%)
Overall Mortality	20 (18%)	25 (22%)	28 (19%)	20 (22%)	7 (12%)

LT in the era of COVID-19 is challenging. Nevertheless, the obstacles are not insurmountable.

Data are either presented as medians (inter-quartile range) or n (%). All figures are rounded to the nearest integer. All percentages are calculated with the cohort size given as the denominator. Non-transplant comparison cohorts are not included in this table. Colmenero et al. (2020), and Dumortier et al. (2020) calculated a composite end-point (admission to ICU, mechanical ventilation, and death) to indicate severe disease. Becchetti et al. (2020) is a multicentre, prospective study recruiting patients from 19 secondary and tertiary liver transplant centres across Europe, with Inselspital, University Hospital of Berne being the coordinating centre. Only patients older than 18 years of age are included. ICU = intensive care unit; NR = not reported; only patients who were eventually discharged had their duration of hospital stay calculated (Table 1).

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