COVID-19 infection in liver transplant recipients: Clinical features and outcomes from a Canadian multicentre cohort

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ABSTRACT

BACKGROUND: Prior studies have assessed risk factors and clinical outcomes in liver transplant (LT) recipients infected with COVID-19 globally; however, there is a paucity of Canadian data. Our multicentre study aims to examine the characteristics and clinical outcomes of LT patients with COVID-19 infection in Canada. **METHODS:** Adult LT recipients with reverse transcription-polymerase chain reaction (RT-PCR) confirmed COVID-19, from Canadian tertiary care centres between March 2020 and June 2021 were included. **RESULTS:** A total of 49 patients with a history of LT and COVID-19 infection were identified. Twenty-nine patients (59%) were male, median time from LT was 66 months (IQR 1–128), and median age was 59 years (IQR 52–65). At COVID-19 diagnosis, the median alanine transaminase (ALT) was 37 U/L (IQR 21–41), aspartate aminotransferase (AST) U/L was 34 (IQR 20–37), alkaline phosphatase (ALP) U/L was 156 (IQR 88–156), total bilirubin was 11 µmol/L (IQR 7–14), and international normalized ratio (INR) was 1.1 (IQR 1.0–1.1). The majority of patients (86%) were on tacrolimus (monotherapy or combined with mycophenolate mofetil); median tacrolimus level at COVID-19 diagnosis was 5.3 µg/L (IQR 4.0–8.1). Immunosuppression was modified in eight (16%) patients post-infection. Eighteen patients (37%) required hospitalization, and three (6%) required intensive care unit (ICU) admission and mechanical ventilation. Four patients (8%) died from complications related to COVID-19 infection. On univariate analysis, neither age, sex, comorbidities, nor duration post-transplant were associated with risk of hospitalization or ICU admission. **CONCLUSIONS:** LT recipients with COVID-19 have high rates of hospitalization but fortunately have low rates of ICU admission and mortality in this national registry.

KEYWORDS: COVID-19; immune suppression; liver transplant

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INTRODUCTION

The SARS-CoV-2 (COVID-19) pandemic has brought significant challenges to clinicians caring for liver transplant (LT) recipients. LT recipients represent a large cohort of immunosuppressed patients with high burden of comorbidities. This puts them at increased risk for severe disease and poor outcomes in the setting of COVID-19 infection (1). Researchers have sought to better understand the risks and clinical outcomes of LT recipients in the United States, Europe, and the Asian Pacific infected with COVID-19. European studies published in early 2020 showed concerning rates of hospitalization and mortality in solid organ transplant recipients, with Miarons et al, finding mortality as high as 37% in their Spanish cohort (2). These results were echoed in the first studies published by Belli et al, which found patients infected with COVID-19 had a mortality rate of 32% (3). However, later studies by the group led by Dr Belli found mortality was closer to 20% and was comparable to propensity matched non-transplant patients (4). Hospitalization rates, on the other hand, are two-fold higher in this population in comparison to the non-LT population (5). To date, there is a paucity of data on this subject from Canadian centres. Thus, our multicentre study aims to examine the characteristics and clinical outcomes of LT patients infected with COVID-19 in Canada.

MATERIALS AND METHODS

Study design, setting, population, and data source

This retrospective cohort study was conducted using data collected from patients with orthotopic LT who were diagnosed with reverse transcription-polymerase chain reaction (RT-PCR) confirmed COVID-19 infection between March 2020 and June 2021. Data was collected from six Canadian tertiary care centres including Edmonton (University of Alberta Hospital), Vancouver (Vancouver General Hospital), Winnipeg (Winnipeg Health Sciences Centre), London (University Hospital), and Montreal (McGill University Health Centre; Centre hospitalier de l'Université de Montréal). Patient data from all centres was collected using electronic health records and chart review. Data on patient demographics, comorbidities, clinical presentation, laboratory data, immunosuppression (including levels, any post-infection adjustments), COVID-19 therapies, rate of hospitalization, intensive care unit (ICU) admission, use of mechanical ventilation, and death was collected. This study was approved at multiple centres in Canada including the Health Research Ethics Board of Alberta (Pro00100705).

Outcomes and definitions

The primary outcomes of interest were rate of hospitalization and mortality. Secondary outcomes included the use and length of mechanical ventilation, type of immunosuppression used and any adjustments post-COVID-19 infection, type of COVID-19 treatment, and the presence of graft dysfunction defined as development of hepatitis (aspartate aminotransferase [AST] or alanine transaminase [ALT] ≥2x the upper limit of normal [ULN]) or cholestasis (alkaline phosphatase [ALP] or total bilirubin ≥2x ULN) or documented allograft rejection. The ULN was defined using sex-appropriate cut-offs (males: ALT 30 U/L, AST 40 U/L, ALP 115 U/L; females: ALT 19 U/L, AST 32 U/L, ALP 100 U/L). For patients with abnormal baseline liver enzymes, these definitions were adapted to reflect change relative to the baseline rather than the ULN.

Statistical methods

Descriptive statistics for the cohort are presented as means with SD for normally distributed continuous variables, medians with interquartile range (IQR) for non-parametrically distributed continuous variables, and proportions for categorical variables. Differences between groups were evaluated using the log rank test. Mean imputation was utilized for missing patient data. Univariable logistic regression was used to identify associations between baseline factors and mortality or hospitalization, expressed as unadjusted odds ratios (OR) with 95% CI. Multivariable modelling was not performed due to the small sample size.

All analyses were conducted using SPSS (version 26.0, SPSS, Chicago, IL, USA) with a p value less than 0.05 considered to be statistically significant.

RESULTS

Patient demographic characteristics

A total of 49 patients with a history of LT and COVID-19 infection were identified; 29 patients (59%) were male, the majority (51%) were Caucasian, and the median age at COVID-19 infection was 59 years (IQR 52–65) (Table 1). The median time from LT was 66 months (IQR 1–128). Hepatitis C infection was the most common transplant indication (37%), followed by hepatocellular carcinoma (33%) and autoimmune liver disease (29%). The most common comorbidities were hypertension (53%), diabetes (49%), dyslipidemia (39%), and ≥stage 2 chronic kidney disease (CKD) (35%). The median BMI was 26 kg/m^2 (IQR 23–31). Most patients (80%) were non-smokers, seven patients were ex-smokers (14%), and three patients were actively smoking (6%). Only 10% of patients had evidence of chronic obstructive pulmonary disease (COPD). The majority of patients (65%) at diagnosis of infection presented with upper respiratory symptoms, only 27% had fever (>38.2°C) and 16% were asymptomatic (Table 2).

Hepatic graft outcomes

At COVID-19 diagnosis, the median ALT was 37 U/L (IQR 21–41), AST was 34 U/L (IQR 20–37), ALP was 156 U/L (IQR 88–156), total bilirubin was 11 µmol/L (IQR 7–14), albumin was 36 (IQR 17–49), INR was 1.1 (IQR 1.0–1.1), and creatinine was 107 (IQR 87–143) (Table 2). The majority of patients were on tacrolimus monotherapy (43%) or a combination of tacrolimus and mycophenolate mofetil (MMF) (43%); median tacrolimus level at COVID-19 diagnosis was 5.3 µg/L (IQR 4.0–8.1). Immunosuppression was modified in 8 patients (16%) post-infection; either the tacrolimus dose was reduced (4%), MMF dose was reduced (4%), or MMF was held (8%). Only one patient developed graft dysfunction, 3 months post-transplant (acute cellular rejection) after MMF was held; this resolved after reinitiation of the pre-existing regimen. There was no report of graft loss.

Treatment, hospitalizations, and mortality

Eighteen patients (37%) required hospitalization, and three (6%) required ICU admission and

Table 1: Demographic characteristics of liver transplant patients with confirmed COVID-19 infection from March 2020 to June 2021 in 6 tertiary care centres across Canada

Demographics	
Median age, y, (IQR)	59 (52–66)
Sex, no. (%)	
Male	29 (59)
Female	20 (41)
Ethnicity, no. (%)	
Caucasian	25 (51.0)
Asian	8 (16)
First Nations	4 (8)
Middle Eastern	4 (8)
Black	3 (6)
Unknown	5 (10)
Comorbidity, no. (%)	
Hypertension	26 (53)
Diabetes mellitus	24 (49)
Dyslipidemia	19 (39)
Obstructive lung disease	5 (10)
Coronary artery disease	12 (25)
Renal insufficiency	17 (35)
Active tobacco use	3 (6)
Median BMI kg/m^2 (IQR)	26 (23–31)
Liver transplant indication,* no. (%)	
Hepatocellular carcinoma	16 (33)
Hepatitis C	18 (37)
Hepatitis B	4 (8)
NASH	6 (12)
Alcoholic liver disease	3 (6)
Autoimmune liver disease	14 (29)
Other	6 (12)
Immunosuppression, no. (%)	
Tacrolimus	21 (43)
Tacrolimus and MMF	21 (43)
Sirolimus	3 (6)
Cyclosporine	2 (4)
Cyclosporine and MMF	2 (4)

**Multiple patients had concomitant transplant indications such as simultaneous HCC and HCV; 'Other' liver transplant indications includes pregnancy related liver disease, congenital/genetic liver disease and cryptogenic cirrhosis*
IQR = Interquartile range; NASH = Non-alcoholic steatohepatitis; MMF = Mycophenolate mofetil

Table 2: Laboratory values and symptoms at diagnosis in LT diagnosed with COVID-19 (*N* = 49)

Presenting characteristics	
Symptoms, no. (%)	
Upper respiratory (cough, dyspnea)	32 (65)
Fever (>38.2° C)	13 (27)
Gastrointestinal (nausea, diarrhea)	2 (4)
Asymptomatic	8 (16)
Laboratory test results, median (IQR)	
Creatinine (µmol/L)	107 (87–143)
Hemoglobin (g/L)	124 (114–136)
Platelet (x 10^9/L)	185 (136–217)
White blood cell (x 10^9/L)	5.6 (3.9–5.6)
ALT (U/L)	37 (20–41)
AST (U/L)	34 (20–37)
ALP (U/L)	156 (87.5–156)
Total bilirubin (µmol/L)	11 (7.5–14)
INR	1.1 (1.0–1.1)
Albumin (g/L)	36 (17–49)

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ALP = Alkaline phosphatase; INR = International normalized ratio of prothrombin

Table 3: Hospitalization, ICU admission, and mortality in liver transplant patients with confirmed COVID-19 infection from March 2020 to June 2021 in six tertiary care centres across Canada (*N* = 49)

Outcomes	
Hospital admission, no. (%)	18 (37)
ICU admission, no. (%)	3 (6)
Mechanical ventilation, no. (%)	3 (6)
Mortality, no. (%)	4 (8)

ICU = Intensive care unit

mechanical ventilation (Table 3). Most patients (75%) were treated with supportive care. Six patients (12%) were treated with dexamethasone, eight patients (16%) received antibiotics, two patients (4%) received remdesivir, and one patient received convalescent plasma. Four patients (8%) died due to complications of COVID-19. On univariate analysis, neither age, sex, nor comorbidities were associated with risk of hospitalization or ICU admission.

DISCUSSION

Early evidence from the pandemic highlighted the increased risk for hospitalization in the LT population, and while these studies also showed an increased risk for ICU admission and death, multiple large prospective and retrospective studies of international cohorts have since shown outcomes of LT patients that were comparable to non-transplant populations (4–7).

We found a high rate of hospitalization (37%) in post-LT patients diagnosed with COVID-19. Only a small proportion of patients required ICU admission (6%). Mortality related to COVID-19 was 8%. Our study is in agreement with the largest geographically analogous study out of the United States by Mansoor et al, who reported a hospitalization rate of 40% and an 8% mortality rate (6). Hepatic graft outcomes within our cohort were, similarly, consistent with prior literature that found low rates of hepatic dysfunction, acute or chronic rejection in LT patients infected with COVID-19 (2–8). There was a relatively elevated creatinine on presentation, which has also been previously reported, and may reflect the risk of pre-renal injury associated with COVID-19 in a population with a high degree of overlapping chronic kidney disease (CKD) (6,8). Due to small sample size, we did not find any association between burden of comorbidity or increased age and risk of hospitalization or mortality. Association between increased comorbidity and older age with hospitalization have been reported in earlier studies (2–8).

Calcineurin inhibitors used alone or in combination with MMF was the most common form of immunosuppressive regimen within our cohort. Only 16% of patients in our cohort had any adjustment to their immunosuppression, with the most common adjustment being temporary holding of MMF. Interestingly, the use of MMF has been shown to have a deleterious effect on hospitalization and mortality; conversely, Tacrolimus use has been shown to have a beneficial impact (3,10). The high incidence of tacrolimus immunosuppression, the low immunosuppressive targets and the remoteness of transplant (on average 55 months) may in part explain the low mortality seen in our cohort.

The changes made to immunosuppression within our cohort were in line with current American Association for the Study of Liver Diseases (AASLD) guidelines (11). In clinical practice, these patients are followed closely and this likely impacts

the rate of hospitalization. In addition, the current literature supports the practice of frequent routine monitoring of liver biochemistry, immunosuppression levels, and renal function in these patients. Previous studies have shown up to a third of LT recipients developed acute kidney injury during infection with COVID-19 and over half required hemodialysis (12).

Limitations of this study include: the retrospective nature of analysis, small numbers of patients included, and missing data. These limitations precluded analysis and comparisons of outcome metrics such as outpatient COVID-19 therapies and the impact on outcomes by date of infection, socioeconomic or geographic characteristics. The majority of patients in our study were infected before the advent of COVID-19 vaccination and many were infected prior to the use of dexamethasone, remdesivir, and monoclonal therapies becoming standard of care. This limits the applicability of our results to the current pandemic landscape. Though this has also been the case for previously published studies assessing outcomes of COVID-19 infection in the post-LT population. It is possible that with current standard of care, and with increased vaccination rates, outcomes in this patient population have improved. Finally, our cohort only captures patients with PCR confirmed infection and thus only reflects patients with symptomatic disease warranting testing and may be skewed towards more severe presentations. However, our estimations of hospitalization and mortality are consistent with or lower than equivalent studies, suggesting this effect is minimal.

In conclusion, we present a cohort of post-LT patients from across Canada infected with COVID-19 and show this group has relatively low rates of ICU admission and mortality. This patient population has higher rates of hospitalizations, which is comparable to other case series, demonstrating that patient outcomes in Canada reflect the experiences of post-LT cohorts in the United States and Europe. We could not identify any patient characteristics associated with hospitalization or ICU admission in our cohort, likely related to low patient numbers. Given the dynamic nature of COVID-19 with new variants, evolving treatments and our growing understanding and armamentarium in the management of infected LT patients, future prospective studies are needed to better elucidate the care of post-LT patients in the COVID-19 pandemic.

ACKNOWLEDGEMENTS: Presented in part at the Canadian Digestive Diseases Week (virtual), March 5, 2022. The authors thank Yashasavi Sachar for help with data collection.

CONTRIBUTIONS: Conceptualization, RA Bhanji; Data Collection, J Chow, M Omar, P Wong, G Huard, EM Yoshida, D Peretz, M Brahmania; Formal Analysis, MK Smith, RA Bhanji; Writing – Original Draft, MK Smith, RA Bhanji; Writing – Review & Editing, MK Smith, J Chow, R Huang, M Omar, M Ebadi, P Wong, G Huard, EM Yoshida, D Peretz, M Brahmania, AJ Montano-Loza, RA Bhanji.

All authors have contributed and approved the final version of this manuscript. RA Bhanji is acting as the article guarantor.

ETHICS APPROVAL: The study has been reviewed by the Health Research Ethics Review Board of Alberta (HREBA).

INFORMED CONSENT: N/A

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL: N/A

FUNDING: No funding was received for this work.

DISCLOSURES: The authors have nothing to disclose.

PEER REVIEW: This manuscript has been peer reviewed.

ANIMAL STUDIES: N/A

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