Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Inferior Liver Transplant Outcomes during early COVID-19 pandemic in United States

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ABSTRACT

Background: : Since its declaration as a global pandemic on March11th 2020, COVID-19 has had a significant effect on solid-organ transplantation. The aim of this study was to analyze the impact of COVID-19 on Liver transplantation (LT) in United States.
Methods: : We retrospectively analyzed the United Network for Organ Sharing database regarding characteristics of donors, adult-LT recipients, and transplant outcomes during early-COVID period (March 11- September 11, 2020) and compared them to pre-COVID period (March 11 - September 11, 2019).
Results: : Overall, 4% fewer LTs were performed during early-COVID period (4107 vs 4277). Compared to pre-COVID period, transplants performed in early-COVID period were associated with: increase in alcoholic liver disease as most common primary diagnosis (1315 vs 1187, $P< 0.01$), higher MELD score in the recipients (25 vs 23, $P<0.01$), lower time on wait-list (52 vs 84 days, $P<0.01$), higher need for hemodialysis at transplant (9.4 vs 11.1%, $P=0.012$), longer distance from recipient hospital (131 vs 64 miles, $P<0.01$) and higher donor risk index (1.65 vs 1.55, $P<0.01$). Early-COVID period saw increase in rejection episodes before discharge (4.6 vs 3.4%, $P=0.023$) and lower 90-day graft/patient survival (90.2 vs 95.1 %, $P<0.01$; 92.2 vs 96.5 %, $P<0.01$). In multivariable cox-regression analysis, early-COVID period was the independent risk factor for graft failure at 90-days post-transplant (Hazard Ratio 1.77, $P<0.01$).
Conclusions: : During early-COVID period in United States, overall LT decreased, alcoholic liver disease was primary diagnosis for LT, rate of rejection episodes before discharge was higher and 90-days post-transplant graft survival was lower.

Background

Starting in late December 2019, Coronavirus disease 2019 (COVID-19) had an explosive spread around the world [1]. COVID-19 pandemic significantly impacted solid-organ transplantation with increased mortality seen in patients on the waitlist and in transplant recipients [2]. Despite the declaration of national emergency, closure of non-essential businesses, and aggressive social distancing measures, we saw a rapid transmission of COVID-19 across United States. During the initial part of the pandemic, the numbers of wait-list registrations and organ donations significantly decreased, which was much more pronounced for kidney transplantation [3–5]. After a brief pause, various centers resumed performing transplantation, albeit cautiously, in selected recipients [6]. The early-COVID period also coincided with the implementation of the new national liver allocation policy [7]. The data regarding outcomes of liver transplantation (LT) performed during the COVID 19 pandemic is limited. The aim of this study was to analyze the impact of COVID-19 pandemic on LT and its outcomes in the US.

Material and Methods

Patients and selection criteria

Patient-level non-identifiable information was retrieved from the nationwide Organ Procurement and Transplant Network managed by

Abbreviations: ALD, alcoholic related liver disease; ALF, acute liver failure; BMI, body mass index; CI, confidence interval; COD, causes of death; COVID-19, Coronavirus disease 2019; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICU, intensive care units; IQR, interquartile range; LT, liver transplant; MELD, model for end-stage liver disease; MV, mechanical ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SE, standard error; UNOS, United Network for Organ Sharing

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the United Network for Organ Sharing (UNOS). We evaluated all patients 18 years of age and older who underwent LT in the United States between 2019 and 2020. We compared the donor and recipient characteristics and transplant outcomes between pre-COVID period (March 11th to September 11th, 2019) and compared them to early-COVID period (March 11th to September 11th, 2020). If a patient had more than one LT during the time period, only their first transplant was included in analysis. This study was considered exempt by the Institutional Review Board.

Patient characteristics and outcome variables

We searched UNOS registry as of March 2021 for recipient demographic data, primary listing diagnosis, co-morbidities, time on waitlist, model for end-stage liver disease (MELD) scores at time of listing and transplant. Evaluable donor characteristics included demographics, donor risk index [8], cold ischemia time and distance between donor and recipient hospital. Numbers and trends of transplants including deceased donors and living donors in all regions and causes of death (COD) in recipients were also reviewed in the UNOS registry.

Statistics

Statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA) and R-Studio using R Version 4.1.1 (R Studio, Boston, MA, USA). Non-parametric analysis was used to compare continuous variables between groups (Mann-Whitney U test 2 groups and for categorical data with the $\chi 2$ test or Fisher's exact test for categorical data). The overall and graft survival were calculated from the date of transplant to the date of event using the Kaplan-Meier method. The log-rank test was used to compare survival curves. Cox regression analysis was applied to assess the association of multiple covariate factors with survival between two groups. Results were presented as hazard ratios (HR) and reported with 95% confidence intervals (CI) and two sided *P* values. The stepwise backward model selection method was used to build the most parsimonious multivariable model. Sensitivity analysis was performed to calculate the E-value [9]. For all statistical analyses, $P<0.05$ was taken as statistically significant.

Results

Liver transplants and its trends

Of the 8,384 individuals who received a LT during the study period, there was a 4% cumulative decrease in a number of liver transplants performed during the early-COVID period (4,107 vs 4,277). This decrease was most pronounced in the months of March-April, 2020 with a rebound in numbers seen from May-July, 2020 (Fig. 1A). Number of liver transplantation performed in each UNOS region is shown in Fig. 1B. During the study period, the total number of liver transplantations decreased in regions of 1, 2, 3, 5, 6 and 8 and the number of liver transplantations increased in region 7, 9, 10 and 11.

Recipient Characteristics

Characteristics of LT recipients are summarized in table 1. As the primary etiology, the number and percentage of alcohol related liver disease (ALD) significantly increased during the early-COVID period [1315 (32%) vs 1187 (28%)], while the number of transplants for hepatocellular carcinoma (HCC) significantly decreased [752 (18%) vs 896 (21%)]. During the early-COVID period, the median waiting list time was shorter (52 vs 84 days, $P<0.001$), the need for dialysis before transplant was higher (11 vs 9.4 %, $P=0.012$) and the median MELD score at the time of listing (21 vs 20, $P<0.001$) and MELD score at time of transplant were higher (25 vs 23, $P<0.001$). For induction immunosuppressive therapy, use of anti-thymocyte globulin decreased (4.6 vs 7.5%, $P<0.001$) and use of basiliximab and steroid increased (24.0 vs 20.7 %, $P<0.001$; 58.5 vs 55.2%, $P<0.001$) during the early-COVID period.

Donor characteristics

During the early-COVID period, the donor body mass index (BMI) was higher (27.3 vs 26.9 kg/m2, $P=0.016$), while median donor age, gender ratio, number of living donors (4.7 vs 5.1%, $P=0.36$) and Hepatitis C virus (HCV) positivity rate (10.3 vs 9.9%, $P=0.55$) were the same. During the early-COVID period, median distance between donor hospital and recipient hospital increased (131 vs 64 miles, $P<0.001$), cold ischemia time was prolonged (5.7 vs 5.5 hour, $P<0.001$), and donor risk index increased (1.65 vs 1.55, $P<0.01$).

Outcomes

The risk of acute rejection prior to discharge was significantly higher in the early-COVID period (4.6 vs 3.4, $P=0.023$) (Table 2). Graft survival at 30-days post-transplantation was statistically lower (95.2 vs 96.6%, $P=0.013$), while 30-days patient survival was the same (96.9 vs 97.8%, $P=0.076$) during the early-COVID period. Graft survival and patient survival at 90-days post-transplantation were significantly lower during the early-COVID period (90.2 vs 95.1 %, $P<0.001$; 92.2 vs 96.5 %, $P<0.001$. This difference became more pronounced after 30 days post-transplantation (Fig. 2A & 2B). COVID-19 was listed as the direct cause of death in 5/155 (3.2%) of total deaths in patients who were transplanted during the early-COVID period. In the cox regression multivariable analysis, early-COVID period (HR 1.77; 95% CI, 1.45-2.17; $P<0.001$), recipient portal vein thrombosis (HR 1.48; 95% CI, 1.11-1.99; $P=0.009$), recipient mechanical ventilation at the time of transplant (HR 1.70; 95% CI 1.18-2.46; $P=0.005$), re-transplant (HR 2.06; 95% CI 1.44-2.96; $P<0.001$), HCV-positive donor (HR 0.67; 95% CI, 0.46-0.99; $P=0.043$), and cold ischemia time (HR 1.10; 95% CI, 1.06-1.13; $P<0.001$) had a significant impact for 90 days graft survival. Other characteristics like recipient age, recipient gender, recipient BMI, pre-transplant diabetes, donor age, donor gender, donor BMI and donor risk index did not impact the outcomes (Table 3).

Sensitivity Analysis

The HR ratio of 1.77 for graft failure could only be explained away by an unmeasured confounder, above and beyond all the currently measured confounders, that was associated with both early-COVID period and 90-day graft loss by a HR of 2.94-fold each. The confidence interval could be moved to include the null only by an unmeasured confounder, above and beyond all the currently measured confounders, that was associated with both early-COVID period and 90-day graft loss by a HR of 2.26-fold each.

Discussion

This study was performed to investigate the impact of COVID-19 pandemic on liver transplantation rates and its outcomes. Using the UNOS database, we describe unique changes in the donor and recipient characteristics, and a higher rate of graft loss during the first 90 days of transplantation during the early-COVID period.

Even before the pandemic, alcohol related liver disease was becoming one of the most common indications of liver transplant in the United States [10]. During the pandemic, overall alcohol consumption and its misuse increased considerably [11, 12]. This led to an increase in hospitalizations from ALD as well as the increase in liver transplants performed for both acute and chronic alcohol

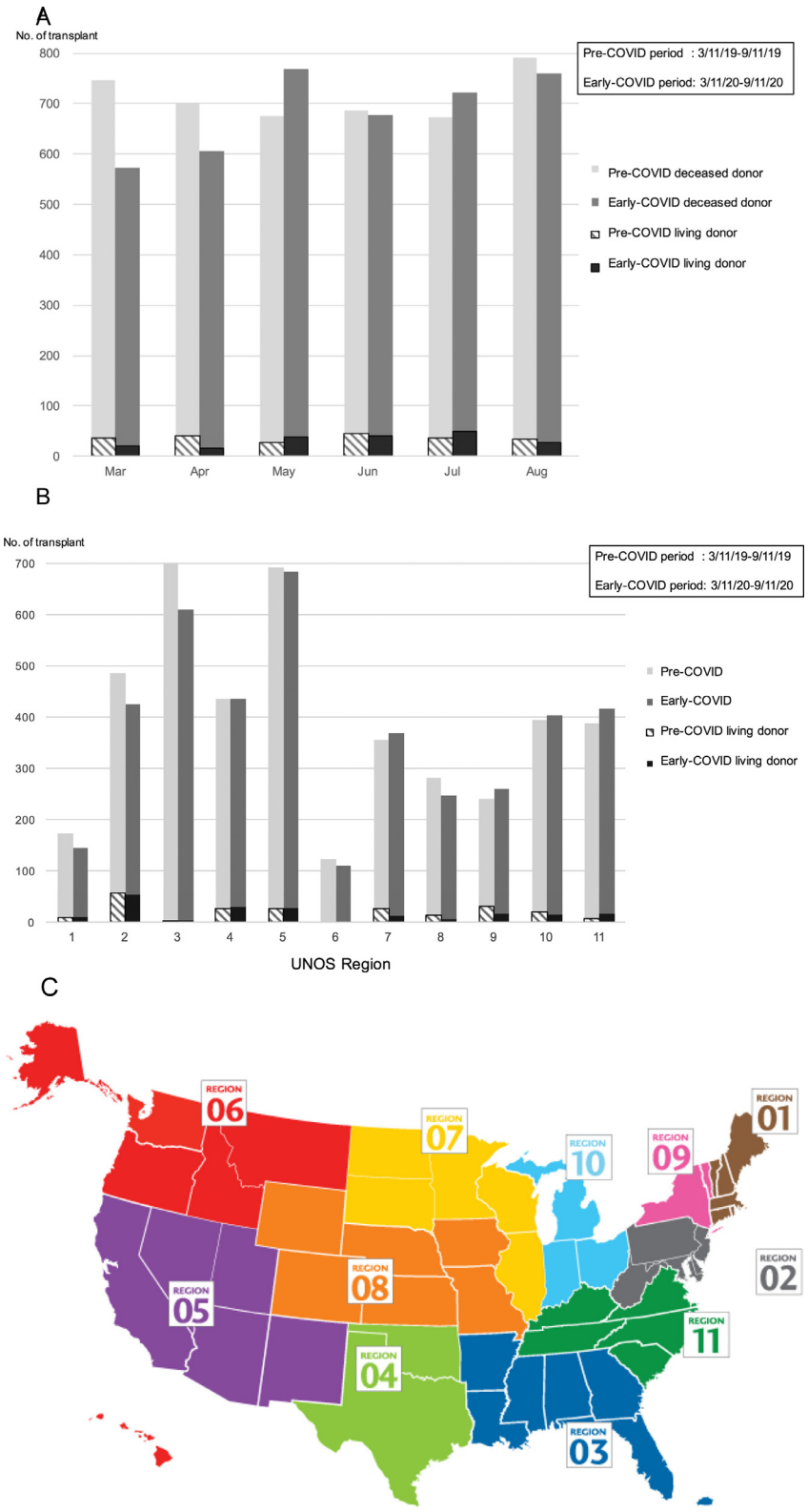

Fig. 1. (A) Monthly trend of liver transplants performed; (B) Variation among UNOS regions in the number of liver transplants performed; (C) UNOS region map.

related liver disease [12]. There was a corresponding decrease in liver transplantations performed for chronic hepatitis-related liver disease and HCC [13, 14].

Very early in the pandemic, due to infectious concerns, most of the transplant centers were performing transplants in fewer and very carefully selected patients [2]. To justify the risk-benefit of performing transplant during a pandemic, these selected patients were usually sicker and had a higher probability of imminent death while waiting for liver transplantation. As previously described in the literature, these sicker patients had an increased need for intensive care and higher incidence of renal dysfunction requiring hemodialysis [15]. This likely resulted in the higher MELD score both at the time

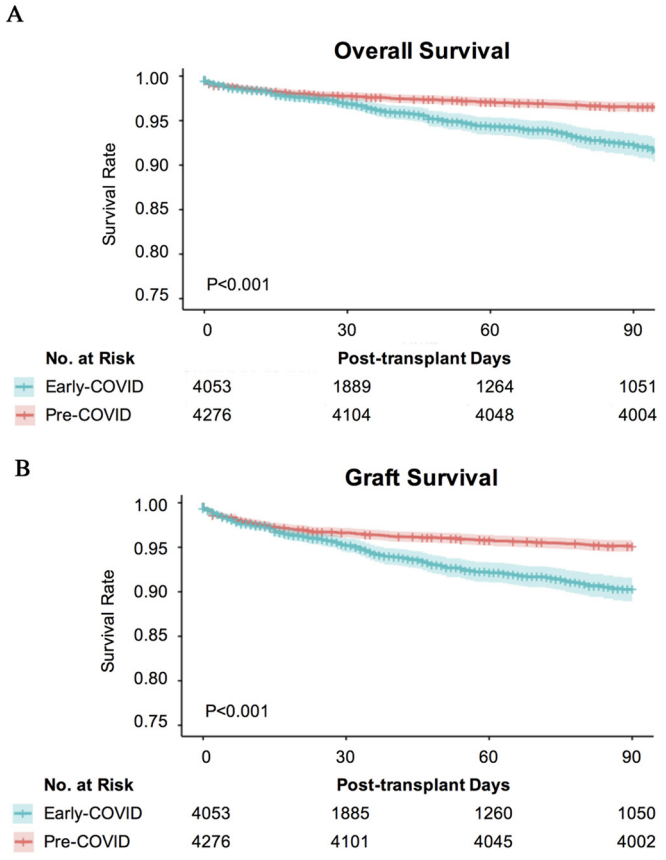

Fig. 2. (A) Comparisons of overall survival between early-COVID and pre-COVID periods. (B) Comparisons of graft survival between early-COVID and pre-COVID periods.

of listing and at the time of transplantation, and a higher incidence of multi-organ (simultaneous liver-kidney) transplants being performed. A decrease in overall wait time during early-COVID period was likely associated with an increase in the number of patients with acute alcoholic liver disease, who because of their progressive and medically non-responsive liver dysfunction, often underwent liver transplantation during their index hospitalization [11]. A decrease in listings and liver transplantations for HCC may also have contributed to a decrease in median MELD and waitlist times during this period.

The decrease in the frequency of LTs performed in US was worse very early in the pandemic, when transplant community had a poor understanding of the disease, and very limited diagnostic and therapeutic options were available [2]. At the same time healthcare facilities especially intensive care units (ICU) were overwhelmed by critically ill patients with COVID. This lead to diversion of resources and hospital beds towards the care of patients with COVID, while routine medical and surgical care suffered as a consequence [16]. Simultaneously many centers paused less urgent transplant surgeries because of lack of ICU beds and resources [16]. Many centers placed a hold on less urgent living donor liver transplants [3]. After the first initial wave of COVID, transplant surgeries slowly resumed and a rebound in number of transplants performed was noted in the following months of May to July, 2020.

In February 2020, the new liver allocation policy was also implemented which allowed for broader sharing of the organs across different organ procurement organizations [7]. This likely contributed to regional change in the number of liver transplants performed, increase in donor risk index, wider distances between donor and recipient hospital and an increase in the cold ischemia time. Long term impact of these factors on the graft outcomes still needs to be determined.

Table 1
Donor and recipient characteristics of liver transplants performed

Variable	Early-COVID n=4107	Pre-COVID n=4277	*P*
Recipient			
Age, years, median (IQR)	58 (48-64)	58 (49-64)	0.134
Age 18-64, n (%)	3132 (76)	3268 (76)	0.873
Age ≧65, n (%)	975 (24)	1009 (24)	
Gender			0.820
Male, n (%)	2622 (63.8)	2741 (64.1)	
Female, n (%)	1485 (36.2)	1536 (35.9)	
Race, n (%)			0.822
White	2873 (70.0)	2971 (69.5)	
Black	307 (7.5)	310 (7.2)	
Hispanic/Latino	680 (16.6)	725 (17.0)	
Asian	167 (4.1)	182 (4.3)	
Primary Etiology, n (%)			0.001
Alcoholic related liver disease	1315 (32)	1187 (27.8)	
Nonalcoholic steatohepatitis	711 (17.3)	775 (18.1)	
Hepatocellular carcinoma	752 (18.3)	896 (20.9)	
Hepatitis C virus	224 (5.5)	265 (6.2)	
Hepatitis B virus	43 (1.0)	45 (1.1)	
Acute liver failure	116 (2.8)	118 (2.8)	
Others	946 (23)	991 (23.2)	
BMI kg/m2, median (IQR)	28.7 (25.0-33.3)	28.7 (25.0-33.0)	0.631
Days on waitlist, median (IQR)	52 (7-234)	84 (13-268)	<0.001
Diabetes, n (%)	1198 (29.2)	1272 (29.8)	0.615
HCV positive status, n (%)	396 (9.9)	495 (11.7)	0.010
Dialysis at transplant, n (%)	457 (11.1)	404 (9.4)	0.012
MV at transplant, n (%)	132 (3.2)	164 (3.8)	0.139
Multi-organ transplant, n (%)	435 (10.6)	402 (9.4)	0.074
Re-transplant, n (%)	161 (3.9)	172 (4.0)	0.823
MELD at listing, median (IQR)	21 (14-30)	20 (12-28)	<0.001
MELD at transplant, median (IQR)	25 (17-32)	23 (15-31)	<0.001
Donor			
Age, years, median (IQR)	39 (29-53)	40 (28-54)	0.270
Age 18-64, n (%)	3846 (94)	3959 (93)	0.046
Age ≧65, n (%)	260 (6)	318 (7)	
Gender			0.128
Male, n (%)	2533 (61.7)	2568 (60.0)	
Female, n (%)	1574 (38.3)	1709 (40.0)	
Race, n (%)			0.011
White	2638 (64.2)	2744 (64.2)	
Black	733 (17.8)	724 (16.9)	
Hispanic/Latino	576 (14.0)	621 (14.5)	
Asian	104 (2.5)	109 (2.5)	
BMI kg/m2, median (IQR)	27.3 (23.7-31.7)	26.9 (23.5-31.1)	0.016
Living Donor, n (%)	192 (4.7)	219 (5.1)	0.363
HCV positive status, n (%)	405 (10.3)	403 (9.9)	0.553
Distance*, miles, median (IQR)	131 (30-286)	64 (8-200)	<0.001
Cold ischemia time, hours (IQR)	5.7 (4.7-7.0)	5.5 (4.4-7.0)	0.004
Donor Risk Index, median (IQR)	1.65 (1.43-1.99)	1.55 (1.34-1.86)	<0.001
Induction immunosuppression			
Anti-thymocyte globulin, n (%)	189 (4.6)	320 (7.5)	<0.001
Basiliximab, n (%)	985 (24)	886 (21)	<0.001
Steroids, n (%)	2402 (59)	2363 (55)	<0.001

COVID: Coronavirus disease 2019, IQR: interquartile range, BMI: Body mass index, MELD: model end-stage liver disease, HCV: hepatitis C virus, MV: mechanical ventilation, Distance*: distance between donor and recipient hospital

During the pandemic, there was a decrease in the overall immunosuppression used for transplant recipients across all transplant centers [17]. Similar trend was noted in our study with decrease in the use of induction immunosuppression using anti-thymocyte globulin. This cautious use of lower immunosuppression, targeted to lower the risk of infection, likely resulted in higher rates of rejection prior to discharge [18]. Data regarding treatment of these rejection episodes and their impact in the longer-term graft survival are unknown.

There was a statistically significant decrease in 90-day graft survival and patient survival in recipients of liver transplants performed during the pandemic when compared to pre-pandemic period. Patient survival starts to decrease more than 30-days post-transplant. Based on the available data, while 90-day deaths from overall

Table 2
Outcomes of liver transplants

		Early-COVID n=4107	Pre-COVID n=4277	*P*
Month, n (%)	March	572 (13.9)	747 (17.5)	<0.001
	April	606 (14.8)	703 (16.4)	
	May	768 (18.7)	676 (15.8)	
	June	678 (16.5)	686 (16.0)	
	July	723 (17.6)	673 (15.7)	
	August	760 (18.5)	792 (18.5)	
Acute rejection before discharge, n (%)		185 (4.6)	146 (3.4)	0.023
Post-transplant length of stay, days, median (IQR)		10 (7-16)	10 (7-16)	0.533
90-day overall survival, (%)		92.2%	96.5%	<0.001
90-day graft survival, (%)		90.2%	95.1%	<0.001

COVID: Coronavirus disease 2019, IQR: interquartile range

Table 3
Multivariable Cox regression analysis of factors affecting 90-days graft survival

Variables	B (SE)	Hazard Ratio (95%CI)	*P*
Early-COVID period	0.57 (0.10)	1.77 (1.45-2.17)	<0.001
Primary Disease			0.073
ALD (REF)			
NASH	0.22 (0.16)	1.24 (0.90-1.72)	0.184
HCC	0.061 (0.16)	1.06 (0.77-1.47)	0.709
Hepatitis C	0.22 (0.23)	1.24 (0.79-1.96)	0.354
HBV	-0.17 (0.59)	0.84 (0.27-2.66)	0.771
Acute liver failure	0.58 (0.25)	1.79 (1.09-2.94)	0.022
Others	0.41 (0.15)	1.50 (1.13-2.01)	0.006
Diabetes of recipient	0.19 (0.11)	1.21(0.97-1.50)	0.092
Recipient portal vein thrombosis	0.39 (0.15)	1.48 (1.11-1.99)	0.009
Mechanical ventilation at transplant	0.53 (0.19)	1.70 (1.18-2.46)	0.005
Re-transplant	0.72 (0.18)	2.06 (1.44-2.96)	<0.001
Hepatitis C donor	-0.40 (0.20)	0.67 (0.46-0.99)	0.043
Cold Ischemia Time (hours)	0.091 (0.015)	1.10 (1.06-1.13)	<0.001

COVID: Coronavirus disease 2019, ALD: alcohol related liver disease, NASH: nonalcoholic steatohepatitis, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, HBV: hepatitis B virus, ALF: acute liver failure, SE: standard error, CI: confidence interval

infection (non-COVID) were lower, deaths from primary non-function of the graft, graft failure, bleeding and multi-organ failure increased. (Supplement table 1). This is likely because of a combination of factors. In early part of the pandemic, before the availability of COVID vaccinations, fresh transplant recipients were at a higher risk of acquiring severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. This acquisition could be from household contacts, community spread or possibly from health care exposure. Direct COVID deaths accounted for 3.2% (5/155) of all the deaths during the 90-days post-transplant period for liver transplants performed during the early-COVID period. Immediately after discharge, transplant recipients require a close and intense follow up. But early in the pandemic, there was severe disruption of routine outpatient care [19] which also impacted the frequency of in-person follow up of fresh transplant recipients and delays in obtaining laboratory and imaging testing. As shown in the regression multivariable analysis, other factors that impacted 90-day graft survival were recipient portal vein thrombosis, mechanical ventilation at time of transplant, re-transplantation and longer cold ischemia time. All these known factors along with impact of unknown risks associated with recidivism in patients transplanted for alcoholic liver disease, and long-term impact of increased graft rejection prior to discharge may also have contributed to overall worse 90-day graft and patient survival.

Limitations

This study was performed retrospectively using UNOS database. Only information related to COVID-19 in the database was the cause of death. Other indirect effects of COVID-19 like psychosocial impact, medication non-compliance, rates of recidivism of alcohol use, rates of community/household spread of COVID-19 are not available in the database and may impact the outcomes.

Conclusion

During the early-COVID period (from March 11, 2020 to September 11, 2020), overall number of liver transplantation decreased, alcohol related liver disease became the primary diagnosis for liver transplantation, rate of organ rejection was higher and 90-day post-transplant graft survival was lower. While lessons learnt during this period have helped the transplant community become more resilient, long-term impact on the outcomes of transplants performed during this period need to be further evaluated.

Author contributions to manuscript

KO, SN and AD contributed to study design, analysis of data and writing of the manuscript. All authors approved the final manuscript.

Conflict of interest

The authors have no conflicts to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.liver.2022.100099.

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