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Clinical Characteristics, Hospitalization, and Mortality Rates of Coronavirus Disease 2019 Among Liver Transplant Patients in the United States: A Multicenter Research Network Study

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Liver transplant (LT) patients represent one of the largest immunosuppressed cohorts. However, outcomes of coronavirus disease (COVID-19) in this population remain poorly defined although liver injury has been reported in patients with COVID-19.[1]

We sought to examine the characteristics of LT patients infected with COVID-19 and study the rates of hospitalization, mortality, thrombosis, or intensive care unit (ICU) requirement in LT with COVID-19 in the United States.

Methods

We used a large health research network (TriNetX) to compile electronic medical records (EMRs) of adult (aged ≥18 years) LT recipients with confirmed severe acute respiratory syndrome coronavirus 2 infection (LT group) from 35 health care organizations in the United States, from January 1, 2020, to June 23, 2020. Within this same time period, we also identified COVID-19–positive patients with no history of LT (non-LT group). For both cohorts, we collected demographics, comorbidities, clinical symptoms, and laboratory findings at COVID-19 diagnosis and presentation. To address confounders, cohorts were balanced using 1:1 greedy nearest neighbor propensity score matching (PSM) based on age, race, and key comorbidities (Table 1).[2] The 4 outcomes of interest were risk of hospitalization (defined as composite outcome of inpatient or critical care services), mortality, thrombosis (defined as composite outcome of deep vein thrombosis, acute pulmonary embolism, stroke, or myocardial infarction), and ICU requirement (requiring mechanical ventilation or extracorporeal membrane oxygenation) after a diagnosis of COVID-19. Further details on methodology are provided in the Supplementary Material.

Results

Between January and June 2020, there were a total of 43,508 non-LT patients with COVID-19 and 126 LT patients with COVID-19 in the database (Table 1). LT patients were significantly older and predominately male and white, and they had a higher prevalence of comorbidities (Table 1). Thus, we performed (1:1) PSM for age, race, and comorbidities. The LT and non-LT groups were relatively balanced after PSM (n = 125 each group) (Table 1).

LT patients were more likely to have nausea and vomiting, malaise and fatigue, diarrhea, and abdominal and pelvic pain. LT patients were more likely to have higher mean levels of creatinine (Cr), total bilirubin, and alkaline phosphatase (Table 1). Within 6 months before diagnosis of COVID-19, 39% of LT patients were receiving prednisone, 9% hydrocortisone, 61% tacrolimus, 37% mycophenolate mofetil, and 8% each azathioprine, cyclosporine, sirolimus, everolimus, and basiliximab (Supplementary Table 1).

Patients in the LT group had a significantly higher risk of hospitalization compared to the non-LT group, both before and after PSM (Table 1). After PSM, in adjusted analysis, 40% of patients in the LT group required hospitalization compared to 23% of patients in the non-LT group (risk ratio [RR], 1.72; $P < 0.0043$). In unadjusted analyses, the risk of mortality (RR, 2.27; $P = .0069$), thrombosis (RR, 3.55; $P < .0001$), and ICU requirement (RR, 2.64; $P = .0013$) was higher in the LT group; however, after PSM, there was no difference in risk of mortality, thrombosis, and ICU requirement between LT and non-LT patients with COVID-19 (Table 1).

Discussion

We found LT patients with COVID-19 to have significantly higher risk of hospitalization but not a higher risk of mortality, thrombosis, or ICU requirement compared to patients without LT and COVID-19 upon adjusted analyses.

This is the largest study of LT patients with COVID-19 in the United States to date, to our knowledge. Yi et al[3] reported 21 solid organ transplant recipients diagnosed with COVID-19, including 3 LT patients, at a US high-volume transplant center. In this study, 33% (1/3) of LT patients required hospitalization compared to 40% in our study, and

Abbreviations used in this paper: **COVID-19, coronavirus disease 2019; Cr, creatinine; EMR, electronic medical record; ICU, intensive care unit; LT, liver transplantation; PSM, propensity score matching; RR, risk ratio.**

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Table 1. Comparison of Medication Use Among Non-LT Patients With COVID-19 and LT Patients With COVID-19, Before 6 Months of Diagnosis of COVID-19

	Before matching				After matching			
Characteristics	LT	Non-LT	RR (95% CI)	*P* value	LT	Non-LT	RR (95% CI)	*P* value
n	126	43,508			125	125		
Demographics								
Age, *y*, mean ± SD	57.08 ± 13.28	50.06 ± 18.66		<.0001	57.03 ± 13.32	59.83 ± 14.71		.116
Female, n (%)	43 (34)	23,844 (55)		<.0001	43 (34)	40 (32)		.687
Male, n (%)	83 (66)	19,576 (45)		<.0001	82 (66)	85 (68)		.687
Unknown sex, n (%)	0	88 (<1)		.6133	0	0		
White, n (%)	73 (58)	19,901 (46)		.0061	73 (58)	71 (57)		.798
Black or African American, n (%)	34 (27)	11,157 (26)		.7308	34 (27)	40 (32)		.4058
American Indian or Alaska Native, n (%)	10 (8)[a]	142 (<1)		<.0001	10 (8)	10 (8)		1
Asian, n (%)	10 (8)[a]	1207 (3)		.0004	10 (8)	10 (8)		1
Native Hawaiian or Other Pacific Islander, n (%)	10 (8)[a]	88 (<1)		<.0001	0	0		
Unknown race, n (%)	13 (10)	11,013 (25)		.0001	13 (10)	10 (8)		.5115
Hispanic or Latino, n (%)	14 (11)	6064 (14)		.3602	14 (11)	13 (10)		.8385
Not Hispanic or Latino, n (%)	78 (62)	18,279 (42)		<.0001	77 (62)	54 (43)		.0036
Unknown ethnicity, n (%)	34 (27)	19,165 (44)		.0001	34 (27)	58 (46)		.0016
Comorbid conditions, n (%)								
Essential (primary) hypertension	29 (23)	4180 (10)		<.0001	29 (23)	23 (18)		.3498
Chronic kidney disease	25 (20)	1411 (3)		<.0001	24 (19)	26 (21)		.7518
Diabetes mellitus	20 (16)	3106 (7)		.0001	20 (16)	20 (16)		1
Nicotine dependence	10 (8)[a]	673 (2)		<.0001	10 (8)	0		.0012
Chronic lower respiratory diseases	10 (8)[a]	2346 (5)		.207	10 (8)	10 (8)		1
Heart failure	10 (8)[a]	1131 (3)		.0002	10 (8)	10 (8)		1
Cerebrovascular diseases	10 (8)[a]	485 (1)		<.0001	10 (8)	10 (8%)		1
Alcohol-related disorders	10 (8)[a]	207 (<1)		<.0001	10 (8)[a]	0		.0012
Dyspnea	10 (8)[a]	4632 (11)		.3246	10 (8)[a]	11 (9)		.8196
Ischemic heart diseases	10 (8)[a]	1438 (3)		.0038	10 (8)[a]	10 (8)[a]		1
Presenting symptoms, n (%)								
Fever of other and unknown origin	12 (10)	4664 (11)		.6647	12 (10)	18 (14)		.2429
Cough	10 (8)[a]	6863 (16)		.0159	10 (8)[a]	17 (14)		.1538
Nausea and vomiting	10 (8)[a]	1122 (3)		.0002	10 (8)[a]	10 (8)[a]		1
Malaise and fatigue	10 (8)[a]	1750 (4)		.0257	10 (8)[a]	10 (8)[a]		1
Diarrhea, unspecified	10 (8)[a]	1493 (3)		.0056	10 (8)[a]	10 (8)[a]		1
Abdominal and pelvic pain	10 (8)[a]	695 (2)		<.0001	10 (8)[a]	10 (8)[a]		1
Acute pharyngitis	10 (8)[a]	1045 (2)		.0001	10 (8)[a]	10 (8)[a]		1
Hypoxemia	10 (8)[a]	2139 (5)		.1177	10 (8)[a]	10 (8)[a]		1

Table 1. Continued

Characteristics	Before matching				After matching			
	LT	Non-LT	RR (95% CI)	*P* value	LT	Non-LT	RR (95% CI)	*P* value
Laboratory test results, mean (SD)								
Sodium, *mEq/L*	135.55 ± 5.03	136.58 ± 5.1		.1262	135.67 ± 5	137.06 ± 6.09		.2015
Creatinine [mass/volume] in serum, plasma, or blood,	2.03 ± 2.07	1.36 ± 1.65		.0021	2.04 ± 2.09	3.14 ± 4.45		.103
Hemoglobin, *g/dL*	10.88 ± 2.41	12.52 ± 2.48		0	10.88 ± 2.41	12.42 ± 2.38		.0018
Platelets, *n/μL*	167.11 ± 103.94	220.64 ± 94.55		0	167.11 ± 103.94	199.18 ± 69.46		.0797
Leukocytes, *n/μL*	6.56 ± 5.42	7.74 ± 5.55		.1219	6.56 ± 5.42	6.76 ± 2.7		.8378
Alanine aminotransferase, *U/L*	57.6 ± 154.56	41.59 ± 99.82		.2507	57.6 ± 154.56	35.87 ± 37.27		.3931
Aspartate aminotransferase, *U/L*	74.06 ± 245.79	55.22 ± 214.63		.5284	74.06 ± 245.79	49 ± 54		.5338
Alkaline phosphatase, *U/L*	152.15 ± 143	88.51 ± 58.23		0	152.15 ± 143	88 ± 74		.0123
Potassium, *mEq/L*	4.28 ± 0.65	3.9 ± 0.58		0	4.29 ± 0.66	4.06 ± 0.8		.1173
Total bilirubin, *mg/dL*	1.61 ± 3.39	0.63 ± 0.86		0	1.61 ± 3.39	0.59 ± 0.27		.0655
Albumin, *g/dL*	3.29 ± 0.82	3.43 ± 0.76		.205	3.29 ± 0.82	3.35 ± 0.68		.7183
Neutrophils, *n/μL*	4.53 ± 5.1	7.51 ± 98.46		.8642	4.53 ± 5.1	5.19 ± 1.86		.512
Body mass index, *kg/m²*	27.74 ± 5.42	30.14 ± 8.11		.118	27.74 ± 5.42	30.45 ± 9.03		.2246
Prothrombin time, *s*	14.94 ± 4.17	14.25 ± 6.76		.6123	14.94 ± 4.17	14.3 ± 4.68		.656
C-reactive protein, *mg/dL*	48.74 ± 63	76.44 ± 86.42		.133	48.17 ± 64.49	102.94 ± 92.72		.0242
Lactate dehydrogenase, *mmol/L*	244.9 ± 90.61	400.01 ± 315.65		.0281	244.9 ± 90.61	394.88 ± 225.85		.008
Ferritin, *ng/mL*	9333.93 ± 35,380.02	22,453.26 ± 76,506.63		.493	93,33.93 ± 35,380.02	23,411.78 ± 89,271.63		.5533
Activated partial thromboplastin time, *s*	34.31 ± 11.8	31.38 ± 10.61		.3014	34.31 ± 11.8	32.9 ± 10.39		.7445
Creatine kinase, *mg/dL*	105.92 ± 63.84	399.89 ± 2840.48		.7091	105.92 ± 63.84	280.08 ± 288.57		.0446
Fibrin D-dimer FEU	2.81 ± 5.97	196.24 ± 949.4		.4995	2.81 ± 5.97	3.31 ± 2.22		.8075
Gamma glutamyl transferase, *U/L*	42 ± 31.11	139.51 ± 174.46		.0814	42 ± 31.11	44 ± 0		.8412
Erythrocyte sedimentation rate	44 ± 31.57	45.44 ± 29.36		.8772	44 ± 31.57	32.6 ± 17.26		.3296
Interleukin 6, *pg/mL*	31.6 ± 0	120.58 ± 389.98		.4711	31.6 ± 0	224.37 ± 277.5		.0414
Procalcitonin, *ng/mL*	2.33 ± 6.39	22.07 ± 485.75		.8978	2.33 ± 6.39	1.21 ± 1.08		.5728
Lymphocytes, *n/μL*	0.79 ± 0.28	0.9 ± 3.14		.9082	0.79 ± 0.28	0.41 ± 0.27		.0058
Outcomes								
Hospitalization	50 (40)	5510 (13)	3.13 (2.52–3.89)	<.0001	50 (40)	29 (23%)	1.72 (1.17–2.53)	.0043
Mortality	10 (8)[a]	1523 (4)	2.27 (1.24–4.12)	.0069	10 (8)[a]	10 (8)[a]	1 (0.43–2.32)	1
Thrombosis	10 (8)[a]	972 (2)	3.55 (1.95–6.46)	<.0001	10 (8)[a]	10 (8)[a]	1 (0.43–2.32)	1
Intensive care	10 (8)[a]	1310 (3)	2.64 (1.45–4.79)	.0013	10 (8)[a]	11 (9)	0.91 (0.40–2.06)	.8196

NOTE. Comparison shown both before and after propensity score matching.
SD, standard deviation.

33% (7/21) of solid organ transplant patients required ICU care compared to 8% in our study.

Belli et al[4] reported the European experience in 103 LT patients with COVID-19 from centers located in Italy, Spain, and France. Although they found fever, cough, and shortness of breath to be the most common presenting symptoms, we found LT patients to have a predominance of nausea and vomiting, malaise and fatigue, diarrhea, abdominal and pelvic pain. These differences in presenting symptoms might be due to differences in study design, methods of data collection, data analyses, and the size of source population. Although 40% of patients in our study were admitted to the hospital and 8% required ICU care, 81% of patients in their study required hospitalization, and 15% were admitted to the ICU. Importantly, 16% of LT patients died in their study compared to a mortality rate of 8% in our study.

Our lower rate of hospitalization and ICU care requirements compared to the European experience likely suggests earlier presentation and/or diagnosis in our patients. Furthermore, ICU requirement in our study was defined as requiring mechanical ventilation or extracorporeal membrane oxygenation, whereas in other studies, the definitions were more liberal, thereby leading to a lower estimate of ICU requirement in our study. Other factors such as increased accessibility to a multidisciplinary post-LT team and decreased threshold of admission for LT patients may also have played a role.

LT patients with COVID-19 had higher mean levels of Cr (2.03), suggestive of acute kidney injury compared to non-LT patients with COVID-19. Approximately 15% to 29%[5] of patients with COVID-19 have been reported to have elevated Cr. Although a significant proportion of LT patients were on calcineurin inhibitors, ACE2 expression in kidney is known to be nearly100-fold higher than in respiratory organs and may increase the risk of acute kidney injury in patients with COVID-19.[6]

In a recent Dutch study[7] of patients with COVID-19 pneumonia admitted to the ICU, 27% developed venous thromboembolism, and 3.7% developed arterial thrombotic events. In our study, the overall rate of thrombosis was 8%. The decreased rates of thrombosis in our study might be due to the differences in the study population because the Dutch study included only patients with COVID-19 pneumonia admitted to the ICU who had severe disease leading to increased inflammatory burden. Ours is one of the first studies in LT patients with COVID-19 to provide data on thrombosis, which appear to be reassuring.

This study is limited by its retrospective nature; the inability to access treatment regimens, if any, for patients with COVID-19; and other information unavailable in the TriNetX database, such as information about socioeconomic status, exposure history, and geographic data of the patient population. In addition, data from EMR-based databases is susceptible to coding errors during the translation of patient information into International Classification of Diseases, 10th Revision, codes. However, TriNetX aggregates data from EMRs in real time, which minimizes errors in data collection and analysis. Furthermore, patients with mild disease who were undiagnosed and did not present to health care organizations were not captured in our study, and thus, our cohort likely represents a relatively severe spectrum of COVID-19. However, compared to prior studies on LT and COVID-19, our estimate of hospitalization and mortality rates in LT might be more precise given our higher sample size in both the LT and non-LT groups with COVID-19.

In conclusion, in one of the largest multicenter network studies on LT and COVID-19 to date, we found LT patients with COVID-19 to have a significantly higher risk of hospitalization but not mortality, thrombosis, or ICU requirement compared to patients without LT and COVID-19 when matched for severity of illness. Given the limitations and retrospective nature of this study, further prospective studies are needed to evaluate the burden of care in LT patients and the long-term outcomes of LT patients with COVID-19.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.09.033.

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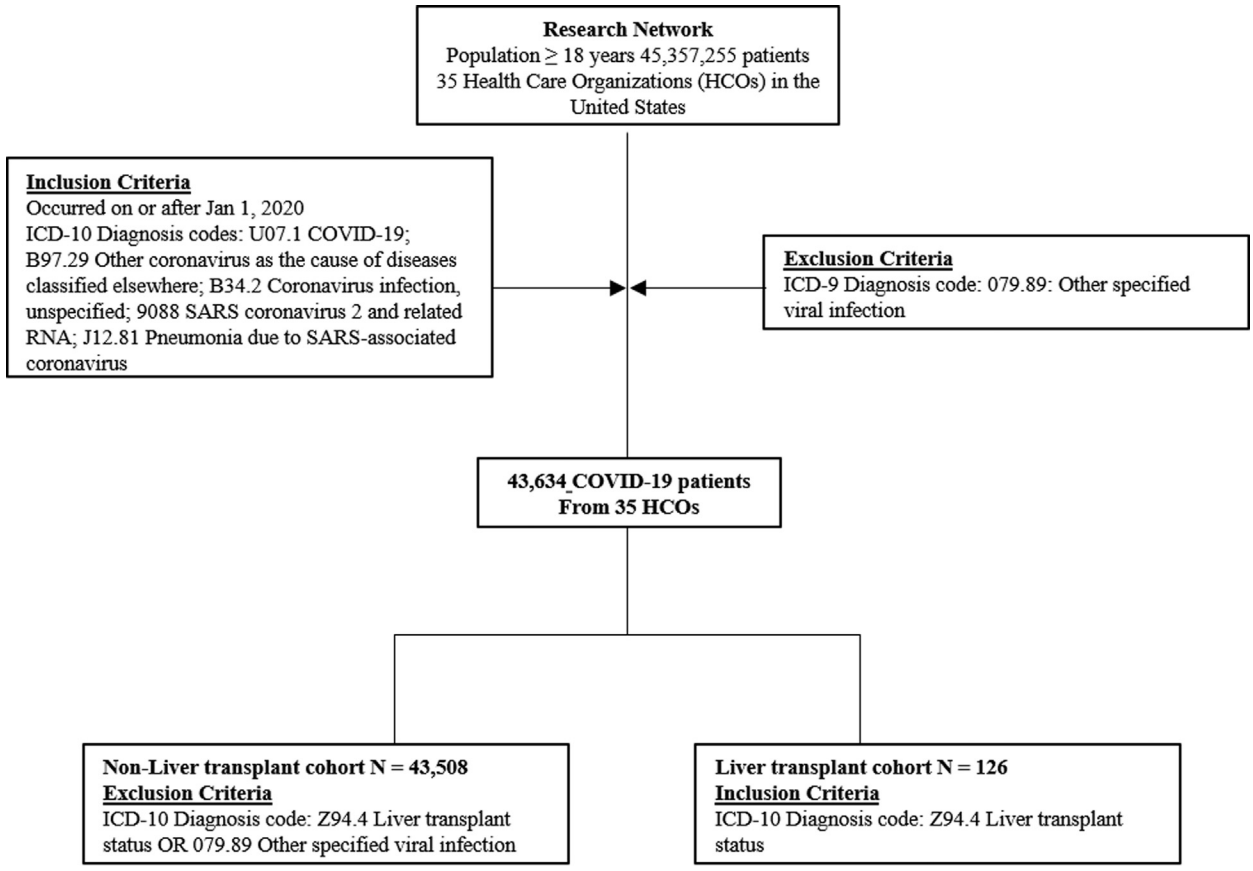
Conflicts of interest
The authors disclose no conflicts.



Supplementary Figure 1. Patient selection protocol in COVID-19 Non-Liver transplant and Liver transplants groups. Patients with ICD-9 code 079.89 were excluded to reduce false positives (occasionally used as a "catch-all' to describe more than 50 viral infections).