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Original Article

COVID-19 in Liver Transplant Recipients

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Abstract

Background and Aims: Coronavirus disease 2019 (COVID-19) has infected over 93 million people worldwide as of January 14, 2021. Various studies have gathered data on liver transplant patients infected with COVID-19. Here, we discuss the presentation of COVID-19 in immunosuppressed patients with prior liver transplants. We also evaluate patient outcomes after infection. ***Methods:*** We searched the PubMed database for all studies focused on liver transplant patients with COVID-19. ***Results:*** We identified eight studies that evaluated COVID-19 infection in liver transplant patients (n=494). Hypertension was the most prevalent comorbidity in our cohort. Calcineurin inhibitors were the most common immunosuppressant medications in the entire cohort. The average time from liver transplant to COVID-19 infection in our cohort was 74.1 months. Fever and cough, at 70% and 62% respectively, were the most common symptoms in our review. In total, 50% of the patients received hydroxychloroquine as treatment for COVID-19. The next most prevalent treatment was azithromycin, given to 30% of patients in our cohort. In total, 80% of the patients were admitted to a hospital and 17% required intensive care unit-level care, with 21% having required mechanical ventilation. Overall mortality was 17% in our review. ***Conclusions:*** Given the immunocompromised status of liver transplant patients, more intensive surveillance is necessary for severe cases of COVID-19 infection. As liver transplantations have been restricted during the COVID-19 pandemic, further investigation is warranted for studying the risk of COVID-19 infection in liver transplant patients.

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Keywords: COVID-19; Liver transplantation; Immunosuppression.

Abbreviations: AASLD, American Association for Study on Liver Diseases; ACE2, angiotensin-converting enzyme 2; AZM, azithromycin; CDC, Center for Disease Control and Prevention; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; HCQ, hydroxychloroquine; HCV, hepatitis C virus; HTN, hypertension; ICU, intensive care unit; IFN-B, interferon-beta; MMF, mycophenolate mofetil; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; SOT, solid organ transplantation; TOZ, tocilizumab; WHO, World Health Organization.

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Introduction

The coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has resulted in over 107 million documented cases globally and close to 2.5 million deaths, as of February 10, 2021.[1] On March 11, 2020, the World Health Organization (WHO) classified COVID-19 as a pandemic.[2] The severity of COVID-19 in the general population ranges from asymptomatic/mild symptoms to critically ill in a proportion of patients.[3] The Centers for Disease Control and Prevention (CDC) has recognized that those with certain underlying medical conditions are at increased risk for severe illness from COVID-19, including cancer, chronic kidney disease, liver disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes mellitus, serious heart conditions, respiratory diseases, and immunocompromised status, including those requiring immunosuppression following solid organ transplantation (SOT).[3]

Accordingly, liver transplantation is the second most common SOT globally after kidney transplantation, with the overall rate reported at 3.7 per million population.[4] In developed countries, hepatitis C virus (commonly known as HCV) is the primary reason for liver transplant; however, HCV is now being replaced by alcoholic liver disease, non-alcoholic liver disease, and hepatocellular carcinoma.[5] Based on familiarity with viral respiratory infections in patients with SOT, the clinical presentation of COVID-19 would likely be more severe in these liver transplant recipients, as they are immunosuppressed and, therefore, have a weaker immune system. To date, no donor-derived COVID-19 cases have been reported. Angiotensin-converting enzyme 2 (often referred to as ACE2), which is a receptor for SARS-CoV-2, is present in almost all organs, including the lung, heart, kidney, liver, and intestine.[6] Therefore, SARS-CoV-2 viremia could potentially infect any transplant organ and suppress itself until the immunosuppressed status exists. In a survey conducted in >80 major transplant centers in the USA between March 24 and March 31, 2020, 31 (35.2%) centers reported 148 patients with SOT with COVID-19 overall.[7] Of these patients, 80 (54.1%) were mildly symptomatic, 31 (20.9%) were moderately symptomatic with pneumonia, and 37 (25.0%) were critically ill. These findings suggest a greater disease severity compared with patients without SOT with COVID-19. Further, SOT recipients who have COVID-19 may shed greater amounts of virus for longer durations compared to non-immunosuppressed patients.[8] This has been shown in other viruses as well, such as influenza. In immunocompetent adults, the majority of patients shed influenza for a maximum of 5 days.[9] Conversely, a study of allogeneic hematopoietic stem cell transplant) recipients with influenza revealed that the mean duration of viral shedding was 7 days (range: 2–37 days); in those patients

who received no therapy, the mean duration of shedding was 11.3 days.[10]

Transplantations have been restricted due to the high risk of serious COVID-19 infection in this population as well as risk of transmission in health care workers. In fact, there has been a steep decline in organ donations and SOT (for kidney, liver, heart, and lung) procedures since the beginning of the COVID-19 pandemic in the USA, decreasing by 51.1%.[11] The American Association for Study on Liver Diseases (commonly known as the AASLD) recommends that liver transplantation should be limited to emergency cases (e.g., patients with high model for end-stage liver disease scores) or hepatocellular carcinoma patients who are at risk of disease progression and removal from the waiting list.[12]

Limited data exist from evaluations of the impact of COVID-19 on liver transplant recipients. In this paper, we review real-world studies evaluating the effect of COVID-19 in liver transplant recipients.

Methods

Search strategy

We searched the PubMed database for all studies focused on liver transplant patients with COVID-19. We used a combination of the keywords 'COVID-19', 'SARS-CoV-2', and 'liver transplant' in our literature search. The PubMed search was limited to articles published on 1/1/2020 or later to ensure the search was more specific to COVID-19 articles only. The search was run on 1/14/2021.

Inclusion and exclusion criteria

We included all studies published in scientific journals that provided information on COVID-19 infection in liver transplant patients. Only studies focused on COVID-19 were included in data collection, and studies discussing SARS, MERS, or other infections were excluded from data collection. Only studies with liver transplant patients were included; papers including non-transplant patients, pediatric papers, and papers without patient data were excluded. Case reports were excluded, as well as papers that did not exclusively focus on liver transplant patients. Only papers with data on five or more patients in their cohort were included. We collected data on country of origin, size of cohort, patient comorbidities, time from liver transplant to COVID-19 infection, immunosuppressant medications, COVID-19 symptoms, COVID-19-specific treatments, hospitalization rate, intensive care unit (ICU) admission rate, need for mechanical ventilation, and mortality rate.

Results

The results of our review of the literature yielded eight studies containing data on liver transplant patients infected with COVID-19 (Fig. 1 and Table 1).[13–20] Patients from our review were from Europe, North America, South America, and Asia. Six studies with patients from Europe were included in our analysis.[13,15–18,20] The total number of patients in our cohort was 494. The largest study we included had 151 patients.[20] The majority of patients were men. The mean patient age was 62.7. Fifty-one percent of patients in our cohort had hypertension as a comorbidity. The next most prevalent comorbidity was diabetes mellitus. Calcineurin inhibitors (CNIs) were the most prevalent immunosuppressant medications among the entire cohort. The next most

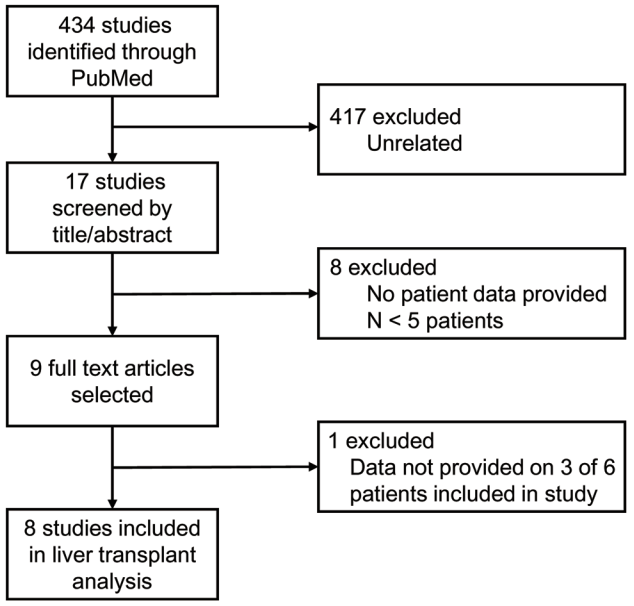

Fig. 1. Flowchart for literatures review of the liver transplant patients with COVID-19 from PubMed.

common immunosuppressant was mycophenolate mofetil (MMF), followed by steroids.

All studies provided data on symptoms, treatments, and outcomes of COVID-19-infected liver transplant patients (Table 2).[13–20] The average time from liver transplant to COVID-19 infection in our cohort was 74.1 months. Fever and cough, at 70% and 62% respectively, were the most common symptoms in our review. In total, 50% of patients received hydroxychloroquine (HCQ) as treatment for COVID-19. The next most prevalent treatment was azithromycin, given to 30% of patients in our cohort. Eighty percent of the entire cohort was admitted to a hospital. Seventeen percent of patients required ICU-level care. Twenty-one percent of patients required mechanical ventilation. Overall mortality was 17% in our review.[13–20]

Webb *et al*[20] reported the largest cohort in our review, with 151 liver transplant patients. Of these patients, 82% were admitted, with 28% requiring ICU-level care. Thirty patients required mechanical ventilation, and twenty-eight patients died. Waisberg *et al*[14] reported data on five patients from Brazil with an average time from liver transplant to COVID-19 infection of 0.56 months, which was the shortest in our cohort. All five of those patients had been admitted and two died. One study reported data on 38 patients from the USA,[19] with 71% of that cohort having been admitted, 21% requiring ICU-level care, and 18% having died.

Discussion

As the COVID-19 pandemic continues to spread and impact the entire world, SOT recipients are at high risk of infection and poor outcomes due to high rates of pre-existing conditions in addition to chronic immunosuppression. Here, we provide one of the largest reviews of COVID-19 in liver transplant recipients. With a median age of 64 years, over 50% and 40% of patients had hypertension and diabetes, respectively, as a comorbidity. The most common immunosuppressive agents used were CNIs (82%), MMF (39%), and steroids (26%). There are inadequate data on the relationship between immunosuppressive therapy and COVID-19

Table 1. Demographic data of COVID-19-infected liver transplant patients

	Study								Summary
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Author[Ref]	Colmenero *et al*[13]	Waisberg *et al*[14]	Becchetti *et al*[15]	Loinaz *et al*[16]	Patrono *et al*[17]	Belli *et al*[18]	Lee *et al*[19]	Webb *et al*[20]	
Country	Spain	Brazil	Europe[c]	Spain	Italy[d]	Europe (Italy, Spain, France)	US	International[e]	
Cohort Size	111	5	57	19	10	103	38	151	Total (*n*) 494; Average (*n*) per study 61.8
Age	Mean 65.3	Mean 59.6	Median 65	Median 58	Mean 65.6	Median 65	Median 63	Median 60	Mean 62.7 Median 64
Sex, M/F	79/32 (71%/29%)	4/1 (80%/20%)	40/17 (70%/30%)	14/5 (74%/26%)	8/2 (80%/20%)	76/27 (74%/26%)	26/12 (68%/32%)	102/49 (68%/32%)	349/145 (71%/29%)
Comorbidities									
HTN	64 (58%)	3 (60%)	32 (56%)	10 (53%)	Unknown	52 (50%)	24 (63%)	63 (42%)	248 (51%)
DM	53 (48%)	1 (20%)	21 (37%)	6 (32%)	Unknown	41 (40%)	18 (47%)	65 (43%)	205 (42%)
Cardiovascular	22 (20%)	0 (0%)	21 (37%)	0 (0%)	Unknown	0 (0%)	11 (29%)	22 (15%)	76 (16%)
CKD	0 (0%)	0 (0%)	16 (28%)	0 (0%)	Unknown	15 (15%)	24 (63%)	0 (0%)	55 (11%)
Other[b]	13 (12%)	1 (20%)	18 (32%)	4 (21%)	Unknown	0 (0%)	2 (5%)	19 (13%)	47 (10%)
Immunosuppressant regimen[a]									
CNI	72 (65%)	5 (100%)	49 (86%)	8 (42%)	10 (100%)	86 (83%)	38 (100%)	135 (89%)	403 (82%)
mTORi	23 (21%)	0 (0%)	6 (11%)	4 (21%)	2 (20%)	0 (0%)	1 (3%)	7 (5%)	43 (9%)
MMF	57 (51%)	4 (80%)	25 (44%)	7 (37%)	6 (60%)	0 (0%)	19 (50%)	77 (51%)	195 (39%)
Steroids	24 (22%)	5 (100%)	10 (18%)	3 (16%)	3 (30%)	0 (0%)	15 (39%)	67 (44%)	127 (26%)
Other	0 (0%)	2 (40%)	1 (2%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	13 (9%)	17 (3%)

Abbreviations: HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; mTORi, mammalian target of rapamycin inhibitors.

[a]Immunosuppressant regimens were grouped as follows: CNI included tacrolimus and cyclosporine; mTORi included everolimus and sirolimus; MMF included MMF and mycophenolic acid; steroids included steroids; and other included basiliximab, anti-thymocyte globulin, and azathioprine.

[b]"Other" included "pulmonary", pulmonary arterial hypertension, "bronchopulmonary", "respiratory", hyperlipidemia, and malignancy.

[c]Becchetti *et al* did not specify which countries in Europe their data came from.

[d]Patrono *et al* did not provide any data on comorbidities.

[e]Webb *et al* collected data from 18 countries, namely the USA, UK, an unspecified Middle East country, Italy, Mexico, Canada, Sweden, Belgium, Netherlands, Brazil, Switzerland, Germany, Egypt, Spain, Greece, India, Philippines, Portugal, and Turkey.

Table 2. Symptoms, treatment, and outcome of COVID-19-infected liver transplant patients

	Study								Summary
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Author[Ref]	Colmenero *et al*[13]	Waisberg *et al*[14]	Becchetti *et al*[15]	Loinaz *et al*[16]	Patrono *et al*[17]	Belli *et al*[18]	Lee *et al*[19]	Webb *et al*[20]	
Country	Spain	Brazil	Europe	Spain	Italy	Europe (Italy, Spain, France)	US	International	
Cohort Size	111	5	57	19	10	103	38	151	Total (*n*) 494; Average (*n*) per study 61.8
Average time from transplant to COVID-19 infection	105 months	0.56 months	72 months	83 months	85 months	Unknown[c]	45.6 months	60 months	Average: 74.1 months
Symptoms									
Fever	83 (75%)	4 (80%)	44 (77%)	8 (42%)	6 (60%)	71 (69%)	23 (61%)	Unknown[d]	239 (70%)
Cough	78 (70%)	2 (40%)	31 (54%)	16 (84%)	3 (30%)	60 (58%)	21 (55%)	Unknown[d]	211 (62%)
Dyspnea	46 (41%)	4 (80%)	26 (46%)	9 (47%)	1 (10%)	35 (34%)	13 (34%)	Unknown[d]	134 (39%)
GI	38 (34%)	1 (20%)	18 (32%)	6 (32%)	1 (10%)	24 (23%)	16 (42%)	45 (30%)	149 (30%)
Treatment									
HCQ	88 (79%)	1 (20%)	24 (42%)	11 (58%)	6 (60%)	63 (61%)	18 (47%)	38 (25%)	249 (50%)
Anti-viral therapy[a]	41 (37%)	0 (0%)	3 (5%)	2 (11%)	2 (20%)	16 (16%)	0 (0%)	19 (13%)	83 (17%)
AZM	60 (54%)	2 (40%)	35 (61%)	0 (0%)	0 (0%)	31 (30%)	18 (47%)	1 (1%)	147 (30%)
Steroids	12 (11%)	0 (0%)	19 (33%)	0 (0%)	3 (30%)	17 (17%)	5 (13%)	0 (0%)	56 (11%)
IFN-B	3 (3%)	0 (0%)	5 (9%)	2 (11%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (2%)
TOZ	15 (14%)	0 (0%)	0 (0%)	2 (11%)	0 (0%)	7 (7%)	0 (0%)	2 (1%)	26 (5%)
Hospital course									
Admitted (*n*)	96 (86%)	5 (100%)	41 (72%)	12 (63%)	9 (90%)	83 (81%)	27 (71%)	124 (82%)	397 (80%)
ICU (*n*)	12 (11%)	Unknown[b]	4 (7%)	1 (5%)	0 (0%)	15 (15%)	8 (21%)	43 (28%)	83 (17%)
Ventilation (*n*)	22 (20%)	2 (40%)	12 (21%)	2 (11%)	2 (20%)	25 (24%)	8 (21%)	30 (20%)	103 (21%)
Death (*n*)	20 (18%)	2 (40%)	7 (12%)	2 (11%)	2 (20%)	16 (16%)	7 (18%)	28 (19%)	84 (17%)

Abbreviations: AZM, azithromycin; GI, gastrointestinal; IFN-B, interferon-beta; TOZ, tocilizumab.

[a]Antiviral therapy included remdesivir, lopinavir/ritonavir, sofosbuvir, and darunavir/cobicistat.

[b]Waisberg *et al* did not provide any data on ICU admissions.

[c]Belli *et al* did not provide any data on average time from transplant to COVID-19 infection.

[d]Webb *et al* did not provide any data on fever, cough, and dyspnea.

in liver transplant recipients with COVID-19. Various studies have shown that CNIs display antiviral effects *in vitro* against coronaviruses and may also ameliorate the cytokine storm.[21,22] Similar to SARS-CoV-2, MMF yields a cytostatic effect on activated lymphocytes; therefore, MMF and SARS-CoV-2 may result in a synergic and damaging outcome on reducing peripheral lymphocytes.[23,24] Although SOT recipients may be at greater risk for COVID-19 due to immunosuppressive therapy, there are still no definitive data to suggest that the immunosuppressive protocol be altered. For patients with mild to moderate COVID-19, it is advised that immunosuppression be continued;[25] however, if there is fever, lymphopenia, or worsening of the patient's pneumonia, reducing the dose of azathioprine or MMF should be considered.[26] Patients with severe COVID-19 may need their dose of CNI reduced. Further research evaluating the role of immunosuppressive agents and COVID-19 is warranted.

As in the general population, the most common symptoms patients had were fever and cough. However, there were also other presentations, including digestive symptoms and dyspnea.[27] The most common treatment for COVID-19 was HCQ. The paradigm of treatment has evolved rapidly, with HCQ now not being recommended for the treatment of COVID-19. We revealed that the overall mortality rate in liver transplant recipients was 17%, which is in alignment with the general population (15–22%).[28,29] However, pooled data from various SOT studies report worse outcomes, with the in-hospital case fatality rate ranging from 24% to 27%.[30,31]

Several limitations of this study should be noted. The majority of patients in our analysis were from European centers; therefore, generalizability to people from other countries may be limited. Moreover, many of the studies included patients treated with HCQ, which is not currently recommended per the Infectious Diseases Society of America COVID-19 guidelines.[32] The use of HCQ, as it was applied in earlier studies, is considered less efficacious than currently available treatments. Furthermore, the cohorts included in this study varied in time from liver transplant to COVID-19 infection (ranging from 0.56 to 105 months), leading to variability in study outcomes. Finally, over or under reporting of symptoms in our various cohorts may have contributed to reporting bias.

In conclusion, patients with liver disease and transplant candidates are at risk from COVID-19. Unfortunately, SOT transplant recipients are a highly susceptible population; therefore, clinicians should have an understanding of the disease and take the essential precautions to ensure the safety of liver transplant recipients.

Funding

None to declare.

Conflict of interest

Ravina Kullar was a former employee of Gilead Sciences. Sammy Saab is on the speaker bureau and honoraria recipient of AbbVie, Bristol Myers Squibb, Bayer, Eisai, Exelixis, Gilead, Intercept, and Salix; Sammy Saab is also an advisor/consultant for AbbVie, Bayer, Eisai, Exelixis, Gilead, Intercept, Mallinckrodt, and Salix. The other author has no conflict of interests related to this publication.

Author contributions

Study concept and design (RK, SS), acquisition of data (RK, APP), analysis and interpretation of data (RK, APP, SS), drafting of the manuscript (RK, APP, SS), critical revision of the manuscript for important intellectual content (RK, APP, SS), statistical analysis (APP), administrative, technical, or material support; study supervision (SS).

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