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Clinical Presentation, Treatment, and Mortality Rate in Liver Transplant Recipients With Coronavirus Disease 2019: A Systematic Review and Quantitative Analysis

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\textbf{ABSTRACT}

Liver transplant recipients may be at increased risk for adverse outcomes with coronavirus disease 2019 (COVID-19) infection because of chronic immunosuppression and associated comorbidities. There is a paucity of literature describing clinical presentation, treatments, and outcomes in liver transplant recipients with COVID-19. A systematic search was performed for articles published up to June 15, 2020, revealing 223 liver transplant recipients with COVID-19 in 15 studies. Patients most commonly presented with fever (66.7%), dyspnea (34.0%), and diarrhea (28.4%). Of these, 77.7% required hospitalization, 24% had mild disease, 40% had moderate disease, and 36% had severe disease. Immunosuppression was modified in 32.8% of recipients. The case fatality rate was 19.3%. Dyspnea on presentation, diabetes mellitus, and age 60 years or older were significantly associated with increased mortality ($P < .01$) with a trend to higher mortality rate observed in those with hypertension and those receiving corticosteroids at the time of COVID-19 diagnosis. The median time from symptoms to death was 11.5 days (2-45 days). In conclusion, liver transplant recipients with severe acute respiratory syndrome coronavirus 2 are overrepresented with regard to severe disease and hospitalizations. Older liver transplant patients with diabetes mellitus or hypertension, who are on maintenance corticosteroids, with a diagnosis of COVID-19 and describing breathlessness should be aggressively monitored for signs of deterioration because of the risk for mortality.

\section*{The clinical presentation of coronavirus disease 2019 (COVID-19) cases and the case-fatality rate has varied significantly between both patient subgroups and countries \cite{1}. Various predictors of disease severity have been identified, including age, cardiovascular disease, cancer, chronic kidney disease, and diabetes \cite{2--7}. However, data on solid organ transplant recipients has been limited to case reports and series \cite{2--8}. The case-fatality rate from COVID-19 ranges widely from 1% to 7.2%, although the rate appears to be much higher for solid organ transplant recipients \cite{9,10}. The clinical course of COVID-19 in liver transplant recipients is variable, with biologically plausible reasons to favor both a reduced and an intensified immunosuppression strategy based on the stage of infection \cite{11}. Further complicating transplant-associated complications is the prevalence of cardiovascular risk in transplant recipients, including hypertension and metabolic syndrome, both of

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which confer increased risk for COVID-19–associated mortality [3,4,6]. Collating and analyzing rapidly emerging data is vital to identify modifiable risk factors to optimize standardized management. We conducted a systematic review to consolidate current literature on clinical presentation, treatment, and outcomes in liver transplant recipients with COVID-19.

METHODS

Data Sources

A literature search was performed through the EMBASE, PubMed, and Web of Science databases up to June 15, 2020. Keywords using Medical Subject Heading, where available, and Emtree Index terms were developed from main subject headings of “COVID-19,” “coronavirinae,” and “liver transplantation.” The search was limited to articles in English. Reference lists of reviewed articles were screened to identify further relevant studies. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [12].

Study Selection

Studies were included if they reported outcomes in liver transplant recipients with confirmed diagnosis of COVID-19 defined as detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on a specimen from the respiratory tract from a symptomatic patient. Studies that did not delineate liver transplantation patients from a cohort of solid organ transplantation recipients, multorgan transplants, and in vitro/animal studies were excluded. Studies reporting the same case were consolidated into 1 data entry.

Data Extraction

Two investigators (J.F. and J.M.) independently searched and extracted relevant articles, which were subsequently verified by the senior investigator (A.N.K.); discrepancies were resolved by consensus. Data were entered into detailed forms and included study design and characteristics, sample size, patient demographics, interval after transplantation, duration of symptoms before diagnosis, baseline immunosuppression, severity of disease, treatment administered, and mortality. Patients were stratified into mild, moderate, or severe, based on a published classification of COVID-19 severity [11]. Quality of data was anticipated to be variable because we predicted the majority of study designs to be case reports or case series.

Clinical Outcome Assessment

The primary objective was to characterize the presenting features of COVID-19 in liver transplant recipients and the case-fatality rate. Secondary objectives were to assess for clinical risk predictors of mortality and the management of baseline immunosuppression strategies with COVID-19 disease severity.

Statistical Analysis

Descriptive statistics were presented as absolute and relative frequencies for categorical variables. Comparisons between 2 groups were performed with the χ² test for categorical data and the Student’s t test or Mann-Whitney U test as appropriate for continuous data. A P value of < .05 was considered statistically significant. Statistical analysis was performed using Stata 13/MP (StataCorp, College Station, Tex, United States). Denominators for baseline characteristics and mortality data varied because of differences in data reporting across studies (Tables 1-3).

RESULTS

The initial search yielded 238 studies. We eliminated 218 studies after initial screening; 15 studies with a total of 223 patients were included in the final analysis. Details of the literature search are reported in Fig 1. These included 4 multicenter registry studies [9,13–15], 5 single-center case series [10,16–19], and 5 case reports [20–25]. Studies included reports from Italy, Spain, France, the United States, and China.

Clinical Characteristics of Liver Transplant Recipients With COVID-19

Among the 223 patients included, 67.8% were over 60 years old and 69.3% were male. The mean age of patients was 59.5 ± 11 years. Of cases that reported on transmission, SARS-CoV-2 was community acquired in 35% of cases, nosocomially acquired in 5%, and unclear or not reported in the remaining. The majority (85.2%) of patients experienced infection ≥ 2 years after transplantation, with only 6 patients [13,19,20,22,23] diagnosed within the first month after transplant (Table 3). One case was thought to represent a potential donor-derived infection, with the recipient developing symptoms on post-transplant day 2 [13,20]. Clinical characteristics of patients are summarized in Table 2. Advanced age (60 years or older) and diabetes mellitus were significantly associated with mortality (P < .001 and P = .01, respectively). Hypertension, body mass index ≥ 25 kg/m², and an immunosuppression regimen that includes corticosteroids at the time of COVID-19 presentation demonstrated a trend toward increased mortality (Table 2).

Clinical Presentation of Liver Transplant Recipients With COVID-19

The majority of patients (77.7%) were hospitalized during the course of illness, with the remainder of patients either managed in the outpatient or setting lacking documentation of hospitalization status. Duration of symptoms before presentation was incompletely reported, although the majority underwent testing for SARS-CoV-2 within 7 days of symptom onset. Using the classifications proposed by Siddiqi and Mehra [11], data on disease severity was available in 76 patients. Of these, 64% of patients had mild-moderate disease and 36% had severe disease. The most common presenting symptoms were fever (67.1%), dyspnea (34.3%), and diarrhea (28.6%) (Table 2). Liver function tests (LFTs) were described only in case reports, which limited quantification and pooling of data. Data pertaining to thoracic imaging were reported in 42.5% of cases. Of these, 94% demonstrated radiologic evidence of COVID-19 on either chest x-ray examination or chest computed tomography (CT).
Table 1. Clinical Characteristics and Mortality in Liver Transplant Recipients With COVID-19

|                  | Overall (N = 223) | Deceased (n = 43) | Survived (n = 180) | P value |
|------------------|-------------------|-------------------|--------------------|---------|
| Age (years), mean (IQR) | 59.6 (61-65) | 64.7 (63-67) | 58.1 (58-65) | .009 |
| Male (%)         | 69.3              | 74.4              | 66.1              | .44    |
| % Aged > 60 y    | 67.8              | 90.7              | 45.0              | <.00001 |

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.

Treatment in Hospitalized Patients With COVID-19

Baseline immune suppression regimen was detailed in 52.0% (116/223) of recipients (Table 2) and was subsequently augmented in 17.0% (38/223) of cases. Of these, there was either a reduction or cessation of antimetabolite in 76.3% (29/38) or calcineurin inhibitor in 52% (20/38) [9,10,14,18-24,26]. A total of 93 of 141 (66%) patients were prescribed hydroxychloroquine, with 35 cases documenting patient survival outcome and no survival benefit trend observed. Six patients received immune modulatory therapy, with 9 patients prescribed interleukin 6 (IL-6) inhibitors and 4 patients receiving systemic interferon (Table 4). Details of therapies, including antivirals, corticosteroids, immunotherapy, and antibiotics against survival outcome are summarized in Table 4.

Predictors of Mortality or Severe Illness in Liver Transplant Recipients With COVID-19

Overall, 43 (19.3%) patients died as a result of complications of COVID-19 [9,10,13-15,18,19,24]. The median duration of time from symptoms to death in hospital was 11.2 days (2-45 days). Age of 60 years or older and diabetes mellitus were significantly associated with increased mortality (P < .01). Hypertension and an immunosuppression regimen that included corticosteroids at the time of COVID-19 presentation demonstrated a trend toward increased mortality (Table 2). Liver transplant recipients presenting with dyspnea were at a significantly higher risk for subsequent COVID-19 related mortality (P < .001). Of the 43 patients who died, all but 3 were 60 years of age or older with multiple comorbidities and all but 5 died at ≥ 1 year after liver transplant.

DISCUSSION

Multiple case series support the concept that recipients of solid organ transplant present with more severe COVID-19 disease, are more likely to require hospitalization, and have a higher mortality rate from COVID-19 compared to their nontransplant counterparts [10,27,28]. This systematic review and quantitative analysis indicates a high mortality rate among liver transplant patients with COVID-19 compared to published reports in the general population [7,29]. Importantly, we found that when recipients of liver transplant with COVID-19 present with dyspnea, a history of diabetes mellitus, and age of 60 years or older, they are at increased risk for mortality (P < .01). These risk factors for subsequent deterioration should serve as critical markers for any clinical teams evaluating recipients of liver transplant with COVID-19 to initiate aggressive monitoring for signs of deterioration.

Liver transplant recipients with COVID-19 experience more severe disease (36%) compared with approximately 6% reported in the general patient population [30,31]. The hospitalization rate in this liver transplant cohort was 77.7%, which is in contrast to rates of age-adjusted hospitalization in non–transplant recipients aged 20 to 29 years from 1.1% up to 18.4% in those older than 80 years [32]. This may be accounted for by the older age of the liver transplant cohort (mean = 59.6 years). The observed case-fatality rate in our liver transplant cohort with COVID-19 was 19.3%, similar to that seen in thoracic transplant recipients [28]. This may be partly because of their older age (mean age = 59.6 years). However, this remains substantially higher than even the 8% mortality rate in an all-comer patient population aged 70 to 79 years [29]. This is substantially higher than the mean case-fatality rate of approximately 1% to 4% in the general population [32,33]. Given the likelihood of severe disease in this patient population, even simple interventions that reduce the risk for COVID-19 acquisition, including social distancing, reduced contact with health services with telemedicine, working from home when possible, and good sanitation, should form an essential component of every transplant program’s anti–COVID-19 response [34].

The most common presenting symptoms reported in liver transplant recipients with COVID-19 are fever and dyspnea,
which is comparable with other transplant subgroups and the broader nontransplant population [27,33]. Importantly, however, in liver transplant patients, dyspnea is a significant risk factor for mortality. Although this may seem intuitive because severe COVID-19 disease is defined by pneumonia and acute respiratory distress syndrome, for which the primary symptom would be expected to be breathlessness, this should serve as an important clinical marker for any clinician reviewing a liver transplant patient with COVID-19, particularly in the early phase of illness. Patients who report any shortness of breath in the context of a SARS-CoV-2 infection should be monitored closely, with consideration for admission to specialized centers for observation and access to intensive care services.

Gastrointestinal symptoms are more prominent in liver transplant recipients with COVID-19 (28.6%) compared with the general population (2%-4%) but are comparable to reports from other solid organ transplant cohorts [9,35,36]. For patients presenting with predominant upper gastrointestinal symptoms, including nausea and vomiting, direct invasion of the central nervous system from the upper respiratory tract with SARS-CoV-2 has been proposed as the mechanism [37]. Lower gastrointestinal tract symptoms and diarrhea are a frequent symptom of other coronaviruses; for example, it is reported in up to 30% of Middle East respiratory syndrome cases [38]. Direct viral invasion of enterocytes causing alteration of intestinal permeability and malabsorption is one of multiple biologically plausible mechanisms [38]. Clinicians assessing liver transplant patients at risk for SARS-CoV-2 should remain vigilant when questioning patients and include gastrointestinal symptoms as part of COVID clinical assessment algorithms.

Because of the heterogeneous nature of reporting in the context of the pandemic, meaningful conclusions regarding the utility of radiologic investigations for the diagnostic

### Table 3. Duration Since Transplantation and Mortality in Liver Transplant Recipients With COVID-19

| Duration Since Transplant | Overall† (N = 203) | Deceased† (n = 43) | Survived (n = 160) | P Value |
|---------------------------|-------------------|--------------------|-------------------|--------|
| < 2 y since transplant (%)| 14.7 (n = 30)     | 11.6 (n = 5)       | 15.6 (n = 25)     | .51    |
| > 2 y since transplant (%)| 85.2 (n = 173)    | 23.8 (n = 38)      | 84.4 (n = 135)    | .51    |

Abbreviation: COVID-19, coronavirus disease 2019.

†Data from Belli et al [15] reported overall outcomes, and did not stratify comorbidities, symptoms on presentation and immunosuppression used based on mortality.

*Data from Pereira et al [9] with severe disease - defined as ICU admission, intubation or death, were presumed deceased in this analysis. (n = 4).

Records identified through Embase (n = 59)
Records identified through PubMed (n = 242)
Records identified through Web of Science (n = 11)
Records identified through other sources (n = 7)

Records after duplicates removed (n = 238)
Records screened (n = 238)
Full-text articles assessed for eligibility (n = 20)
Studies included in qualitative synthesis (n = 15)
Studies included in quantitative synthesis (meta-analysis) (n = 15)

Records excluded (n = 218)
- Not liver transplantation specific
- Not discussing novel SARS-CoV-2 strain
- Guidelines for practice, not clinical reports

Full-text articles excluded due to:
- No transplant cases detailed
- Not discussing novel SARS-CoV-2 strain (n = 5)

Fig 1. Flow diagram of systematic search process.
**Table 4. Therapies Instituted for Liver Transplant Patients Diagnosed With COVID-19**

| Hydroxychloroquine (n = 35) | Author | Deceased* | Author | Survived (n = 24) |
|-----------------------------|--------|-----------|--------|------------------|
| Fernández-Ruiz et al [10] (n = 1) | Administered day 1 after symptom onset | Fernández-Ruiz et al [10] (n = 3) | Administered days 1, 3, and 8 after symptom onset |
| Pereira et al [9] (n = 4) | Day administered not stated. Duration of treatment 5 days | Lagana et al [20] (n = 1) | Administered day 1 of diagnosis |
| Lee et al [18] (n = 6) | Administered hydroxychloroquine | Pereira et al [9] (n = 8) | Day administered not stated. Duration of treatment 5 days |
| | | Lee et al [18] (n = 12) | Administered hydroxychloroquine |

**Antivirals (n = 5)**

| Author (n = cases) | n = 2 | Author (n = cases) | n = 3 |
|--------------------|-------|--------------------|-------|
| Huang et al [24] (n = 1) | Lopinavir/ritonavir + Umifenovir | Qin et al [14] | Oseltamivir |
| Fernández-Ruiz et al [10] (n = 1) | Lopinavir/ritonavir | Zhong et al [23] (n = 1) | |
| Liu et al [25] | Oseltamivir | Umifenovir + Lopinavir/ritonavir |

**Antibiotics and Antifungals (n = 36)**

| Author (n = cases) | n = 7 | Author (n = cases) | n = 29 |
|--------------------|-------|--------------------|-------|
| Huang et al [24] (n = 1) | Piperacillin/tazobactam | Qin et al [14] (n = 1) Zhong et al [23] (n = 1) | Cefoperazone + Sulbactam sodium |
| Pereira et al [9] (n = 3) | Cefoperazone-sulbactam + caspofungin | Liu et al [25] (n = 1) | Cefoperazone |
| Lee et al [18] (n = 3) | Meropenem + Voriconazole | Pereira et al [9] (n = 6) | Azithromycin |
| | | Lee et al [18] (n = 12) | Azithromycin |
| | | Donato et al [16] (n = 9) | Unspecified “antibiotic therapy” |

**Corticosteroid Therapy (n = 8)**

| Author (n = cases) | n = 6 | Author (n = cases) | n = 2 |
|--------------------|-------|--------------------|-------|
| Fernández-Ruiz et al [10] (n = 1) | Methylprednisolone | Liu et al [25] (n = 1) | Methylprednisolone |
| Pereira et al [9] (n = 1) | Bolus dose of corticosteroid | Pereira et al [9] (n = 1) | Bolus dose of “steroid” |
| Lee et al [18] (n = 4) | Commenced IV corticosteroid therapy |

**Immunotherapy (n = 6)**

| Author (n = cases) | n = 3 | Author (n = cases) | n = 3 |
|--------------------|-------|--------------------|-------|
| Fernández-Ruiz et al [10] (n = 1) | Interferon alfa | Liu et al [25] (n = 1) | IVIg, Interferon alfa |
| Fernández-Ruiz et al [10] (n = 1) | Interferon beta | Pereira et al [9] (n = 1) | Interferon beta |
| Pereira et al [9] (n = 1) | Tocilizumab (IL-6 antagonist) | Fernández-Ruiz et al [10] (n = 1) | Tocilizumab (IL-6 antagonist) |

Abbreviations: IL, interleukin; IVIg, intravenous immunoglobulin.

*Four patients recorded by Pereira et al [9] as having “severe disease - defined as ICU admission, intubation or death,” were assumed deceased.
evaluation of liver transplant patients presenting with suspected COVID-19 could not be made in this analysis. Of the 51 patients who had radiologic findings reported, 94% of these had radiographic or CT findings suggestive of a diagnosis of COVID-19. However, these radiologic changes included unilateral or bilateral patchy consolidation, pleural effusions, or hypostatic changes, the differential diagnoses of which remain broad, particularly in the immunocompromised. Whether radiologic scans, particularly CT, maintain their diagnostic utility [39].

In the initial evaluation of patients may have limited diagnostic utility [19,20,22–25]. Only 6 studies detailed the results of liver biochemistry, with no measurable trends reportable [19,20,22–25]. The prevalence of abnormal liver function tests in 1267 COVID-19–positive patients pooled from 12 studies was 19%, with more severe disease associated with liver injury [40]. There are plausible mechanisms for liver injury because the angiotensin-converting enzyme inhibitor 2 receptor used by the SARS-CoV-2 virus for cellular entry is expressed on hepatocytes and cholangiocytes [20,41]. Deranged alanine aminotransferase, platelets, and albumin have been associated with higher mortality in COVID-19 in nontransplant patients, but whether these derangements are directly or indirectly virally mediated or similarly associated with mortality risk in liver transplant is unknown [42]. Four patients included in the review were considered clinically to have developed acute cellular rejection as evidenced by LFT derangement, but only 1 underwent allograft biopsy. Lagana et al [20] described a 5-month-old infant who underwent transplant from a living donor who was found to be COVID-19 positive in the days after donation. The recipient then became febrile on post-transplant day 4 with hypoxia, necessitating noninvasive ventilatory support with subsequent SARS-CoV-2 detected from the respiratory tract. On post-transplant day 6, when hepatic LFT derangement was noted, an allograft biopsy identified histologic features thought to be most consistent with acute cellular rejection and immunosuppression. Paradoxically, LFTs worsened with immunosuppression and only improved with rapid corticosteroid taper and discontinuation of mycophenolate mofetil (MMF). Although it is unproven, the authors speculated that in the absence of other alternative cause the deranged LFTs observed were more likely to represent SARS-CoV-2–mediated hepatitis rather than rejection based on the atypical clinical response to immunosuppression. Although hepatocellular injury in the context of severe COVID-19 infection has been well described elsewhere, determining the exact mechanisms mediating hepatocellular injury in the context of multiple possible confounders at time of critical illness remains challenging [43]. Interestingly, similar nonspecific hepatic injury as described in the allograft biopsy of this case has been noted in the histopathologic examination of liver tissue on postmortem tissue from deceased COVID-19 patients [44].

Recipients of liver transplant who are 60 years of age or older and presenting with a diagnosis of COVID-19 are associated with a 3-fold greater risk for COVID-19–related mortality compared to their counterparts younger than 60. Older age is a well-described risk factor for both severe disease and in-hospital mortality in COVID-19 [2–5]. A diagnosis of diabetes mellitus at presentation with COVID-19 is also associated with a statistically significant 2-fold greater risk for mortality in liver transplant recipients, which is consistent with prior reports in nontransplant patients [3,4]. Diabetes is a well-described risk factor for mortality in infections and in the context of COVID-19 has been associated with a more than doubled risk for intensive care unit admission and tripled risk for death in hospitalized COVID-19 patients in meta-analysis [45,46]. Because liver transplant recipients are overrepresented with regard to cardiometabolic risk profile, attention should be paid by clinicians to glycemic control in the context of the COVID-19 pandemic as a possible modifiable risk factor in this patient cohort [47,48].

An immune suppression regimen that included corticosteroids at the time of COVID-19 diagnosis demonstrated a trend to increased mortality in liver transplant recipients; however, it is difficult to draw conclusions because of confounding factors. Whether a corticosteroid-containing regimen is a surrogate marker for patients who are earlier post-transplant and therefore more immunosuppressed and thus more likely to have metabolic complications known to increase COVID-19 mortality or there is some alternative reason is unclear. There is a preference to reduce immunosuppression in liver transplant recipients at time of COVID-19 diagnosis, with nearly a quarter of patients prescribed a reduction of baseline immunosuppression. Interestingly, there are in-vitro data to support the anti-coronavirus properties of various antirejection medications. While cyclosporin has demonstrated anti-SARS coronavirus 2003 (SARS-CoV) properties by blocking translocation of nuclear factors from T cells into the cytosol [11,49], 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), and MMF have demonstrated anti–Middle East respiratory syndrome proteolytic properties [50,51]. Although various institutional approaches to immune suppression management have been described [27], there presently remains insufficient evidence to guide any standardized approach to the augmentation of immunosuppression in transplant recipients diagnosed with COVID-19.

There are several limitations of this review, including the variability in the detail of data recorded, the extrapolation
of data from cohort studies, and the inability to use meta-analysis techniques. Furthermore, reporting bias is likely to lead to an overestimation of transplant recipients with a heightened disease severity. We report a low proportion with COVID-19 diagnosed early after liver transplant. This may be due to both donor and recipient COVID-19 peri-transplant testing protocols in addition to reduction in the net number of transplants undertaken during the pandemic. A further limitation is our assumption that the liver transplant patients with severe disease reported by Pereira et al [9] died in the intensive care unit. Although this accounts for only 4 patients, this may skew the interpretation of therapeutic interventions and survival benefit given the small sample sizes. The COVID-19 outcome data are continually changing, and thus reports of any delayed mortality in liver transplant recipients have yet to be published. A clear need for systematic and centralized data collection and analysis is highlighted in this study. Transplant centers are encouraged to collaborate with international registries to facilitate further study in this patient population [14] (https://covidcirrhosis.web.unc.edu and https://covid-hep.net).

CONCLUSION
COVID-19 manifests with a similar illness in liver transplant as it does in other transplant recipients and in the non-immune suppressed, but it is more likely to manifest with concurrent diarrheal symptoms. Older patients with dyspnea and diabetes mellitus are at a higher risk for mortality, and in these patients more intensive monitoring for deterioration should be undertaken because case fatality reaches nearly 23%. Data are currently insufficient to guide optimal immunosuppression and COVID-19-directed therapeutic strategies.

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