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Outcomes of COVID-19 in 24 hospitalized liver transplant recipients: an observational study

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Abstract

Background Although liver transplant (LT) recipients are considered a population at risk of severe features of coronavirus disease 2019 (COVID-19), data in this regard are scarce and controversial. In this study, we reported the outcome of 24 cases of LT recipients who were hospitalized due to COVID-19 and investigated the role-playing factors in the severity of the disease.

Methods In this single-center, analytic case-series study, eligible patients were among LT recipients who were hospitalized due to the diagnosis of COVID-19 based on positive results of polymerase chain reaction. Participants were categorized as severe COVID-19 if they were admitted to the intensive care unit, experienced respiratory failure demanding mechanical ventilation, or eventually died. Demographic and clinical data, COVID-19 symptoms and specific treatments, laboratory biomarkers, and immunosuppressive regimens and their alteration during the admission were recorded. Analysis was done using SPSS software.

Results Twenty-four hospitalized LT patients were included, of which nine had severe and fifteen had non-severe COVID-19. Out of 9 patients with severe COVID-19, four sadly died. The analysis and comparison between the two groups revealed longer hospital stays ($P=0.02$), lower lymphocyte counts ($P=0.002$), and higher levels of C-reactive protein (CRP) ($P=0.006$) in patients with severe COVID-19. Patients with non-severe COVID-19 had higher doses of tacrolimus and mycophenolate in their baseline immunosuppressive regimen (both $P=0.02$).

Conclusion Lymphopenia and high CRP levels are associated with more severe forms of COVID-19 in LT patients. Mycophenolate may have protective properties against severe COVID-19. The role of severity indicators in LT patients with COVID-19 needs to be systematically recognized.

Keywords Liver transplantation, COVID-19, immunosuppressive agents, Transplant recipients

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for coronavirus disease 2019 (COVID-19) which was declared a pandemic by Word Health Organization (WHO) On 11 March 2020. COVID-19 presentations vary from mild flu-like symptoms to more severe forms and life-threatening conditions such as multi-organ failure (MOF) and acute respiratory distress syndrome (ARDS) [1]. Notably, certain demographic groups, including the elderly, males, individuals with underlying disorders including hypertension and diabetes, and those with immune dysfunction, are at higher risk of experiencing severe features of COVID-19 [2].

Current evidence suggests the cytokine storm as the key underlying mechanism attributed to the severe COVID-19, characterized by the unleased production of inflammatory cytokines such as IL-1, IL-6, and TNF-α [3]. Following the invasion of SARS-CoV-2 to respiratory epithelial cells, it provokes the synthesis of proinflammatory cytokines in an uncontrolled manner leading to cytokine storm and subsequent deleterious events such as MOF and ARDS [3, 4].

As liver transplant (LT) recipients undergo lifelong immunosuppression, they should be under special consideration due to impaired immunity [5]. Remarkably, multiple studies have indicated that LT recipients do not necessarily face a higher risk of COVID-19 infection or associated complications and mortality compared to the general population [6–9]. Evidence also indicates that chronic treatment with immunosuppressive agents in LT recipients may inhibit the inflammatory cascade and cytokine storm, potentially preventing severe forms of COVID-19 [10]. Nonetheless, immunosuppressives may prolong the replication phase of virus infections, increase the viral load, and delay the full recovery [10, 11]. In a meta-analysis in 2021, the comparison of mortality rates between 610 LT recipients and 239,704 non-LT patients with COVID-19 from 4 studies revealed no significant difference (odds ratio [OR]=0.8, p=0.14). Although the hospitalization rate was reported higher in LT recipients compared to non-LT patients (OR=1.99, $p<0.001$), the ICU admission rates were almost similar (OR=1.35, p=0.55) [8].

Some studies have tried to investigate the contributing factors to the prognosis and severity of COVID-19 in LT recipients, including demographic characteristics, blood biomarkers, comorbidities, and immunosuppressive regimens [1, 11, 12]. High levels of C-reactive protein (CRP) and IL-6 and low absolute lymphocyte count, as well as older age and concomitant diabetes and hypertension, have been shown to be significantly associated with worse outcomes of COVID-19 in LT recipients [11, 12].

However, the role of immunosuppressives in LT recipients with COVID-19 has been a matter of debate. Although the use of calcineurin inhibitors (CNIs) is generally accepted and seemingly not associated with worse outcomes [13], Colmenero et al. declared that mycophenolate mofetil may increase the risk of severe COVID-19 and they encouraged mycophenolate withdrawal or switching to CNIs [11]. Similarly, Forns and colleagues recommended mycophenolate withdrawal in LT patients with COVID-19 at any stage of the disease [14]. On the other hand, in a study in India, the administration of open-label mycophenolate 360 mg daily for a month in patients with COVID-19 was associated with a significant reduction in mortality and hospital stay [15]. Furthermore, the anti-viral effect of mycophenolate against SARS-CoV-2 has been observed in an in vitro study [16].

In spite of current findings, the role of immunosuppression and other clinical/laboratory parameters in the outcome of COVID-19 in LT recipients is not systematically recognized and demands further investigations. In this case-series study, we explored the outcomes of 24 LT patients who were hospitalized due to COVID-19. Additionally, we have investigated the potential contributing factors to the severity of COVID-19 among our LT patients.

Methods

This is a single-center, analytic case series study conducted at Firouzgar University Hospital in Tehran, Iran. The transplantation unit of Firouzgar Hospital began liver transplantation in July 2019. Eligible participants were adult (above 16 y/o) LT recipients who were hospitalized due to COVID-19, from July 2020 to July 2022, at Firouzgar Hospital. The diagnosis of COVID-19 was based on a positive result of real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) for SARS-CoV-2, from the nasopharyngeal swab. Patients were admitted to the hospital at the discretion of an infectious disease specialist based on clinical status and laboratory findings. All 24 patients have had their liver transplantation at Firouzgar Hospital and have been under lifelong surveillance by the transplant unit. All transplant recipients undergo life-long monitoring through regular visits and laboratory check-ups by the transplant team and physicians. Furthermore, patients are well-instructed to inform the transplant team in case of emerging any medical conditions. All data regarding each patient were accessible in electronic or physical files and were extracted by the research team. We made phone calls to patients or their reliable relatives in case of missing information/data in their hospital medical files.

We recorded demographic/clinical data, laboratory parameters, vaccination history, underlying diseases, etiology of liver damage, interval since transplantation,

immunosuppressive regimen at baseline and during admission with adjustments, and COVID-specific treatments for all patients. Vaccinated patients were among those who received at least one dose, prior to the COVID-19 infection, of one of the WHO-approved vaccines available in Iran. Based on the severity of COVID-19 patients were classified into severe and non-severe groups. Patients who were admitted to the intensive care unit (ICU), experienced acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, or eventually expired have been classified as severe. This classification of severity has been supported by previous studies [11]. The primary endpoint of our study was to report the outcome of COVID-19 in our patients. The assessment and comparison of clinical/laboratory findings in our patients in severe and non-severe COVID-19 groups were the secondary endpoints.

Statistical analysis

Qualitative variables are reported as frequencies and continuous variables are expressed as mean ± SD or median as needed. The analysis of categorical variables or proportions was done using Fisher's exact test. For continuous variables, we performed independent samples T-test or Mann-Whitney U-test depending on the normality of data distribution. Statistical analysis was performed using IBM SPSS Statistics 18.0 (SPSS, Inc., Chicago, IL, USA). The significance level in all tests is P-value < 0.05.

Results

All 24 participants were Iranian adult liver transplant recipients with a positive PCR for SARS-CoV-2. Participants were between 17 and 68 y/o with a mean age of 48.29 ± 13.55. Sixteen patients (66.7%) were male and 8 (33.3%) were female. Only 1 patient in the non-severe group was a smoker. The frequencies of diabetes and hypertension in our patients were 6 (25%) and 3 (12.5%), respectively. The history of vaccination against COVID-19 was positive in 10 (41.6%) patients which 7 (70%) of them were vaccinated before transplantation.

We recorded the initial presentations of COVID-19 at the time patients were referred to the infectious diseases outpatient clinic, or primary COVID-19 manifestations during transplant hospitalization. Gastrointestinal symptoms were the most frequent complaints (33%), and then cough (29.2%), dyspnea (29.2%), fever (25%), malaise (20.8%), headache (16.7%), and sore throat (12.5%).

The causes of liver damage in study subjects included primary sclerosing cholangitis (PSC) in 7 (29.2%), hepatitis B in 5 (20.8%), hepatitis C in 1 (4.2%), Wilson disease in 1 (4.2%), non-alcoholic steatohepatitis (NASH) in 4 (16.7%), alcoholic hepatitis in 2 (8.3%), and other etiologies of liver damage in 4 (16.7%) patients. None of our patients had a diagnosed cardiovascular or lung disease.

Ten patients (41.6%) were infected during the admission for transplantation and none of them was infected by donor liver.

Based on the severity of COVID-19, 9(37.5%) patients were categorized in the severe group which 5(55.5%) of them were ICU admitted, and unfortunately, 4(44.4%) were expired. The comparison of demographics and clinical data between severe and non-severe groups revealed no statistically significant differences, except for the length of hospitalization which was significantly longer in the severe group ($P=0.02$) (Table 1).

The key findings regarding each patient within severe and non-severe COVID-19 groups are demonstrated in additional file 1 and additional file 2, respectively. All mortality cases were among new LT recipients who were infected with SARS-CoV-2 during the admission for transplantation.

The values of laboratory biomarkers measured in non-severe and severe COVID-19 groups during their admission are summarized in Table 2. Patients with severe COVID-19 had significantly higher levels of CPR compared to the non-severe group ($P=0.006$). We measured the absolute lymphocyte counts of our patients at the beginning of admission and also the lowest (minimum) lymphocyte counts all through the admission. Although no significant difference at the beginning (onset) counts were reported ($P=0.1$), patients in the severe group had significantly lower lymphocyte counts at the minimum levels compared to the non-severe group ($P=0.002$). Among COVID-19-specific treatments, significantly more patients in the severe group received IVIG compared to non-severe (4 vs. 1, respectively, $P=0.04$).

We recorded the baseline immunosuppressives and their daily dose in addition to immunosuppressive regimens during hospital admission for patients within each group. Significantly more patients with non-severe COVID-19 had mycophenolate in their baseline regimen ($P=0.02$). Furthermore, the mean baseline dose of mycophenolate and tacrolimus were significantly higher in the non-severe group compared to the severe group (both $P=0.02$) (Table 2).

Of all LT patients, 13 (54.2%) had mycophenolate at their baseline immunosuppressive regimen. During the COVID-19 admission, mycophenolate in 9 (69.2%) patients were completely withdrawn, in 2 (15.4%) was reduced, and in 2 (15.4%) was continued without dose alteration. Only 2 (15.4%) patients from those who had baseline mycophenolate developed severe COVID-19; one of them was completely withdrawn from mycophenolate, and in one another, mycophenolate was continued without dose reduction.

Table 1 Demographics and clinical data of 24 hospitalized LT recipients with COVID-19 in severe and non-severe groups

Variable	Non-severe *N*=15	Severe *N*=9	*p*-value
Age (mean ± SD)	45.67 ± 14.54	52.67 ± 11.11	0.228
Gender (male)	12 (80%)	4 (44.4%)	0.099
Past medical history			
Diabetes	5 (33.3%)	1 (11.1%)	0.351
hypertension	2 (13.3%)	1 (11.1%)	1
Vaccination against COVID-19 (yes)	7 (46.6%)	3 (33.3%)	0.678
Smoking	1 (6.6%)	0	1
Interval since transplantation			
Month (median)	7.87 ± 9.70	2.44 ± 5.57	0.068
Hospitalization period (days)	12.67 ± 9.53	24.33 ± 13.19	0.020*
Etiology of liver damage			
Alcoholic hepatitis	1 (6.6%)	1 (11.1%)	1
Hepatitis B	2 (13.3%)	3 (33.3%)	0.326
Hepatitis C	1 (6.6%)	0	1
Wilson disease	1 (6.6%)	0	1
PSC	5 (33.3%)	2 (22.2%)	0.669
NASH	2 (13.3%)	2 (22.2%)	0.615
Others	3 (20%)	1 (11.1%)	1
Clinical presentation of COVID-19			
Fever	3 (20%)	3 (33.3%)	0.635
Cough	4 (26.6%)	3 (33.3%)	1
Dyspnea	3 (20%)	4 (44.4%)	0.356
Headache	3 (20%)	1 (11.1%)	1
Gastrointestinal	5 (33.3%)	3 (33.3%)	1
Sore throat	3 (20%)	0	0.266
Others	3 (20%)	2 (22.2%)	1

*Statistically significant

LT, liver transplant; PSC, primary sclerosing cholangitis; NASH, non-alcoholic steatohepatitis

Discussion

In this article, we have evaluated the outcomes and a wide range of potential role-playing factors in the severity of COVID-19 in 24 hospitalized LT patients. We had 15 LT patients with non-severe COVID-19 who did not experience respiratory failure demanding mechanical ventilation or critical clinical status leading to ICU admission or death. The remaining 9 patients were considered severe COVID-19 in which 4 of them sadly expired.

A prospective cohort study conducted by Colmenero et al. in 2020 included 111 LT recipients, of which 35(31.5%) met the criteria of severe COVID-19. Older age ($P=0.038$), dyspnea as an initial COVID-19 presentation ($P<0.001$), receiving bolus corticosteroids and tocilizumab for COVID-19 treatment ($P=0.007$ and $P<0.001$, respectively), and lower lymphocyte counts ($P=0.013$) were significantly more common in the severe COVID-19 group. Regarding immunosuppressive, they reported mycophenolate in the baseline regimen more commonly in patients with severe COVID-19 compared to the non-severe group ($P=0.014$). Besides, mycophenolate was identified as an independent predictor of severe COVID-19 (relative risk (RR): 3.94, 95% confidence interval (CI): 1.59–9.74) [11]. We had the same results regarding lymphocyte counts in our subjects, but surprisingly, we found that mycophenolate was significantly more frequent in the baseline regimen of non-severe group ($P=0.03$), furthermore, they had a higher mean dose of baseline mycophenolate compared to the severe COVID-19 group ($P=0.02$) (Table 2).

Mycophenolate mofetil impedes lymphocytic proliferation by inhibiting DNA replication in T and B lymphocytes; adding to the COVID-19-induced lymphopenia and lymphocyte dysfunction, continuing mycophenolate in LT patients with COVID-19 might lead to poor outcomes and serious risks [5, 17]. However, some studies have shown the antiviral properties and beneficial effects of mycophenolate in patients with COVID-19 including faster recovery, reduced mortality, and COVID-19 complications [15, 18]. In a study by Kato et al., significant anti-SARS-COV-2 activity for mycophenolic acid was observed, which suggests the potential clinical use of mycophenolate in the treatment of COVID-19 [16].

Table 2 Laboratory biomarkers and immunosuppressive regimens in 24 hospitalized LT recipients with COVID-19 in severe and non-severe COVID-19 groups

Variable	Non-severe *N* = 15	Severe *N* = 9	*p*-value	95% Confidence Interval	
				Lower	Upper
Laboratory parameters					
WBC (max) (count/μl)	14.05 ± 6.02	16.12 ± 9.02	0.50	-8.41	4.27
Lymphocyte (onset) (count/μl)	1.37 ± 1.31	1.48 ± 2.74	0.10	-1.82	1.60
Lymphocyte count (min) (count/μl)	0.79 ± 0.94	0.22 ± 0.13	0.002*	-0.10	1.22
PT (max) (sec)	17.78 ± 5.82	24.37 ± 8.79	0.05	-12.75	-0.42
AST (max) (ng/ml) (unit/L)	207.60 ± 475.82	430.44 ± 585.08	0.06	-675.99	230.30
ALT (max) (ng/ml) (unit/L)	182.47 ± 217.48	349.67 ± 442.58	0.29	-445.55	111.15
Bill (max) (ng/ml) (mg/dL)	2.52 ± 2.66	5.28 ± 4.78	0.12	-6.57	1.05
ALB (min) (g/dL)	3.21 ± 0.78	2.600 ± 0.75	0.07	− 0.073	1.30
ESR (max) (1st /hr) (mm/hr) (*N* = 17)	43.55 ± 27.93	36.00 ± 27.67	0.60	-22.58	37.67
CRP (max) (mg/dL) (*N* = 21)	45.43 ± 54.22	145.71 ± 78.10	0.006*	-161.08	-39.48
Covid specific treatments No. (%)					
HCQ	2 (13.3%)	2 (22.2%)	0.61		
Remdesivir	8 (53.3%)	6 (66.6%)	0.67	-	-
Methylprednisolone (pulse)	5 (33.3%)	4 (44.4%)	0.67		
IVIG	1 (6.6%)	4 (44.4%)	0.04*		
Tocilizumab	0	2 (22.2%)	0.13		
Baseline immunosuppressive No. (%)					
Tacrolimus	11 (73.3%)	3 (33.3%)	0.09		
Everolimus	2 (13.3%)	1 (11.1%)	1	-	-
Mycophenolate	11 (73.3%)	2 (22.2%)	0.03*		
Cyclosporin	0	1 (11.1%)	0.37		
Corticosteroid	11 (73.3%)	4 (44.4%)	0.21		
Baseline immunosuppressive dose(mg/day)					
Tacrolimus	3.13 ± 2.38	1.00 ± 1.58	0.02*	0.27	3.99
Everolimus	0.30 ± 0.84	0.167 ± 0.50	0.83	-0.50	0.77
Mycophenolate	1133.33 ± 949.39	326.67 ± 648.38	0.02*	61.37	1551.95
Cyclosporin	0	22.22 ± 66.66	0.19	-73.46	29.02
Corticosteroid	11.47 ± 8.95	6.67 ± 8.66	0.18	-2.93	12.53
Immunosuppressives during hospitalization No. (%)					
CNI	5 (33.3%)	1 (11.1%)	0.35	-	-
CNI + Everolimus	3 (20%)	2 (22.2%)	1		
CNI + Mycophenolate	5 (33.3%)	3 (33.3%)	1		
CNI + Everolimus + Mycophenolate	2 (13.3%)	3 (33.3%)	0.32		

*Statistically significant

LT, liver transplant; WBC, white blood count; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Bill, bilirubin; ALB, albumin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HCQ, hydroxy chloroquine; IVIG, Intravenous immunoglobulin; CNI, calcineurin inhibitor

A meta-analysis in 2020 comprising 24 studies and 3099 patients showed a significantly lower lymphocyte count in patients with COVID-19 who experienced ARDS ($P<0.001$), were admitted to ICU ($P=0.02$), and died ($P<0.001$). Their results also indicate that patients with lymphopenia are more likely to experience severe COVID-19 (OR:3.70, 95%CI:2.44–5.63, $p<0.001$) [19]. Various mechanisms have been hypothesized to explain the lymphopenia in severe cases of COVID-19, including SARS-COV-2-induced apoptosis/proptosis of lymphocytes, bone marrow and thymus suppression, immune-mediated elimination of infected lymphocytes, sequestration of lymphocytes in target organs, and lymphopenia induced by cytokine storm and high levels of blood lactic acid [20, 21].

Regarding calcineurin inhibitors (CNIs), according to the previous studies on LT patients with COVID-19, starting or continuing CNIs or switching to CNI from other immunosuppressives is not associated with any poor outcome or increased mortality [10, 13]. We found that the average dose of tacrolimus in baseline regimen of non-severe COVID-19 group was significantly higher than severe group ($P=0.02$), and more patients in non-severe group had tacrolimus in their baseline regimen

than in severe group, even though statistically not significant ($P=0.09$) (Table 2).

The results yielded by previous studies regarding the treatment with systemic corticosteroids in COVID-19 have been highly controversial [22, 23]. This controversy might be attributed to the use of different types of corticosteroids in studies, the stage of the disease during which corticosteroids were administered, other concomitant treatments received by patients, the incidence of adverse events associated with corticosteroids (such as hyperglycemia, delayed wound healing, and an increased risk of infection and gastrointestinal bleeding), variations in hospital facilities between low-income and high-income countries, and other confounding factors [23]. While the administration of corticosteroids during the inflammatory phase of COVID-19 has established a significant reduction in mortality and incidence of ARDS [24], patients who were under chronic corticosteroid therapy at the time of COVID-19 infection, seem to have a greater risk of mortality and severe COVID-19 [10]. In a multicenter cohort study on 1726 patients with non-severe COVID-19, the administration of corticosteroids was associated with worse clinical outcomes [25]. Overall, using systemic corticosteroids might be more beneficial in severe cases of COVID-19 [26]. We did not yield any results indicating worse outcomes with corticosteroids (Table 2).

The records of vaccination among our patients revealed no statistical difference between the two groups of severe and non-severe COVID-19 (Table 1). However, the beneficial effects of vaccination against COVID-19 in LT recipients are well established [27–29]. According to the previous meta-analysis studies, the humoral response rate following the first dose of vaccination has been estimated to be 22.4–22.5% in LT recipients, and this rate increases over 90% after the third dose [27]. Besides, LT patients seem to have a better response to vaccination compared to other solid organ recipients [28]. However, a study involving 143 LT recipients and 58 control subjects conducted by Toniutto and colleagues, revealed that the immunogenicity of anti-SARS-COV-2 vaccine in LT patients without a previous history of COVID-19 was significantly lower compared to controls. They have also identified mycophenolate as the main predictor of vaccination failure in LT recipients [30]. In addition to mycophenolate mofetil, male gender, coexisting comorbidities, and using more than two immunosuppressants have been associated with poor response to vaccination against COVID-19 in LT recipients [27, 29].

CRP is primarily produced by hepatocytes in response to inflammatory cytokines and is known as a biomarker of acute inflammation. An increased level of CRP is usually observed in inflammatory conditions, mainly in infections [31]. Our laboratory results showed significantly higher levels of CRP among LT patients with severe COVID-19, which is consistent with previous studies [12, 32]. Interestingly, the role of CRP in COVID-19 might go further than a simple indicator of severe inflammation, and CRP could intensify the disease severity by immune dysregulation and organ damage [33]. In addition to CRP, high levels of lactate dehydrogenase (LDH), D-dimer, IL-6, and IL-10 have also been known as severity markers of COVID-19 [12, 34].

Conclusion

lymphopenia and high levels of CRP are associated with more severe forms of COVID-19 in LT patients. Mycophenolate mofetil does not necessarily aggravate the clinical status in LT patients with COVID-19, and may even have protective properties against severe COVID-19. The role of severity indicators, including clinical, paraclinical, and laboratory parameters, along with the role of immunosuppressives in LT patients with COVID-19 needs to be systematically recognized.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Author contributions

A.S. writing and editing the original manuscript & data analysis & data curation & conceptualization & methodologyM.Mansourian. editing the manuscript & project administration & conceptualization & final approval of the manuscriptM.R. editing the manuscript & project administration & conceptualization & final approval of the manuscriptS.K. collecting data, writing the original manuscriptM.N. data analysisS.Z. editing the manuscript & conceptualizationF.H. collecting data & preparing tablesM.Mohammadi. collecting data & preparing tables.

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Data availability

All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethics approval and consent to participate

This study is approved by the ethics committee of Iran University of Medical Sciences (Number: IR.IUMS.FMD.REC.1401.180.) informed consent to participate in this study was obtained from all subjects or their legal guardians.

Consent for publication

Not applicable.

Conflict of interest

Authors have no conflict of interest to declare .

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