



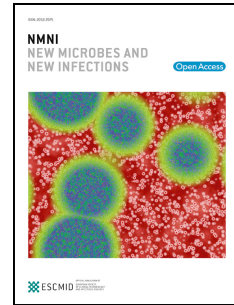
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Incidence, characteristics, and outcome of COVID-19 in patient on liver transplant program: a retrospective study in north of Iran

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PII: S2052-2975(21)00099-8

DOI: <https://doi.org/10.1016/j.nmni.2021.100935>

Reference: NMNI 100935

To appear in: *New Microbes and New Infections*

Received Date: 10 May 2021

Revised Date: 29 July 2021

Accepted Date: 9 August 2021

Please cite this article as: Samidoust P, Esmaeili Delshad MS, Talemi MN, Mojtahedi K, Samidoust A, Jahangiri S, Ashoobi MT, Incidence, characteristics, and outcome of COVID-19 in patient on liver transplant program: a retrospective study in north of Iran, *New Microbes and New Infections*, <https://doi.org/10.1016/j.nmni.2021.100935>.

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Title page

**Incidence, Characteristics, and Outcome of COVID-19 in Patient on Liver Transplant Program: A
Retrospective Study in North of Iran**

Running title: COVID-19 in Liver transplant patients

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1 **Incidence, Characteristics, and Outcome of COVID-19 in Patient on Liver Transplant Program: A**
2 **Retrospective Study in North of Iran**

3 **Running title:** COVID-19 in Liver transplant patients

4 **Abstract:**

5 The risk of severe coronavirus disease-2019 (COVID-19) disease seems to be higher in individuals with solid organ
6 transplantation. Therefore, the purpose of the present research is investigating the incidence of COVID-19 and
7 laboratory data and epidemiologic factors in liver transplant recipients and the patients on the waiting list for liver
8 transplantation. In this study, we evaluated the records of patients on the waiting list for liver transplantation and
9 recipients of liver transplant. Demographic data, underlying disease, history of drug use and participants' outcomes
10 were collected. The diagnosis of SARS-CoV-2 infection for all patients was confirmed using a nasopharyngeal swab
11 specimen with real-time RT-PCR .During the study period, 172 patients were enrolled, among whom 85 patients
12 (49.4%) were on the waiting list for liver transplantation and 87 patients (50.6%) were recipients of liver transplant .
13 Out of them, 10 (5.8%) had a positive result for SARS-CoV-2. Of these patients, 7.05% (6/85) and 4.6% (4/87) of
14 patients on the waiting list and recipients of liver transplant were positive for SARS-CoV-2, respectively. Patients on
15 the waiting list with COVID-19 infection had higher median of albumin, ALT, AST, TBIL, DBIL, HDL and LDL
16 value. In summary, the incidence of COVID-19 in liver transplant patients was slightly high. The existence of
17 underlying liver diseases should be well known as one of the poor predictive factors for worse outcomes in patients
18 with COVID-19. So, comparative studies are recommended to identify risk factors for COVID-19 in patients with
19 liver injury.

20 **Key words:** COVID-19, liver transplant recipients, SARS-CoV-2, Iran

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26 **Introduction:** The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the factor for development of
27 coronavirus disease-2019 (COVID-19), initially observed in Wuhan, China in 2019. It has had a quick spread in the
28 world. In a similar way to this family's previous members, COVID-19 generally results in respiratory tract infection
29 that might be severe, asymptomatic, or mild (1-4). The main symptoms of this disease include fatigue, fever, dry
30 cough, and sometimes nausea, shortness of breath, vomiting, and diarrhea. As preliminary data indicates, the severity
31 of disease has some predictors, such as hypertension, old age, diabetes mellitus, chronic liver and kidney disease, and
32 coronary artery disease (5-8). The severity of the disease is mild in most patients, still, the risk of severe COVID-19
33 disease seems to be higher in individuals with solid organ transplantation, like liver transplants, due to receiving
34 lifetime immunosuppressive therapy and their chronic immunosuppressed state (6, 9).

35 Since the angiotensin-converting enzyme-2 (ACE2) receptor is present in the biliary epithelial and liver cells, the liver
36 has been identified as a potential target for COVID-19 infection. Liver enzymes' elevation is a presentation of this
37 disease that is mainly observed in those admitted in the hospital with an incidence range of 14-53.1% (10).

38 The range of case-fatality rate from COVID-19 is extensive as 1-7.2%, despite the rate appearing much higher for
39 recipients of solid organ transplants (9). Nevertheless, the COVID-19 outcomes and epidemiology among recipient's
40 liver transplanted are confined to case series and case reports (11). There are few early descriptive case series and case
41 reports of recipients solid organ transplantation (SOT) suffering from COVID-19, suggesting poor outcomes.
42 However, it is not known that whether it is different from COVID-19 in the non-transplant population (11-14). Various
43 interventions were conducted in recipients of liver with COVID-19, such as withdrawal and reduction of
44 immunosuppression, treating with empirical anti-viral agents like lopinavir/ritonavir, chloroquine, umifenovir, and
45 remdesivir, and high-dose glucocorticoids (15, 16). Thus, more all-embracing research is required for defining
46 potential risk factors in patients with underlying liver diseases for the development of severe COVID-19.

47 The purpose of the present research is investigating the incidence of COVID-19 and laboratory data and epidemiologic
48 factors in liver transplant recipients and the patients on the waiting list for liver transplantation admitted to referral
49 transplant center (Razi University Hospital) located in the North of Iran, Rasht, Iran.

50 **Methods**

51 This study was approved by the research ethics committee of Guilan University of Medical Sciences, Rasht, Iran with
52 number code IR.GUMS.REC.1399.135. Also, the patients' informed consent to be allowed to use their medical
53 information was obtained.

54 In this retrospective study from June to September 2020, we evaluated the records of 85 patients on the waiting
55 list for liver transplantation and 87 recipients of liver transplant who were admitted to referral transplant center (Razi
56 University Hospital) located in the North of Iran, Rasht, Iran.

57 Of all patients, demographic data including age, sex, past medical history and underlying disease (e.g., primary
58 sclerosing cholangitis (PSC), diabetes, cryptogenic, Non-alcoholic steatohepatitis (NASH) and Hepatitis B (HBV)),
59 laboratory parameters including routine biochemical, and liver function tests data (alanine aminotransferase (ALT),
60 aspartate aminotransferase (AST), and low-density lipoproteins (LDL), High-density lipoprotein (HDL) Vitamin D,
61 direct bilirubin (DBIL), total bilirubin (TBIL) and albumin were investigated. In addition, history of drug use (use of
62 antiviral drugs and immunosuppressive medications) and participants' outcomes (death or recovery) were collected
63 from the electronic patient files. The diagnosis of any liver diseases was confirmed via patients' previous documents.
64 Also, the records of subjects with considerable lacking of data and lost to follow-up were excluded.

65 The diagnosis of SARS-CoV-2 infection was confirmed using a nasopharyngeal swab specimen with real-time RT-
66 PCR or in subjects of negative RT-PCR, a chest computed tomography scan (CT scan) with a high level of suspicion.
67 Demographic data and variable as categorical variables were described as frequencies and percentages. The mean and
68 standard deviation (SD) were carried out to describe continuous variables and qualitative data. All analyses were
69 conducted using SPSS version 18.

70 **Results**

71 During the study period, 172 patients were enrolled, among whom 85 patients (49.4%) were on the waiting
72 list for liver transplantation and 87 patients (50.6%) were recipients of liver transplant. The mean age of patients was
73 47 ± 15.2 . The male subjects were 49 (57.6%) on the waiting list for liver transplantation and 59 (67.8%) in recipients
74 of liver transplant groups. Moreover, 100% and 66.7% of patients on the waiting list and recipients of liver transplant
75 were over 45 years old, respectively.

76 Out of the 172 patients who were enrolled in current study, 10 (5.8%) had a positive result for SARS-CoV-2. Of these
77 patients, 7.05% (6/85) and 4.6% (4/87) of patients on the waiting list and recipients of liver transplant were positive
78 for SARS-CoV-2, respectively. On the other hand, 66.7% (4/6) and 33.3% (2/6) of recipients of liver transplant with
79 COVID-19 were over and under 45 years, respectively. All patients on the waiting list with COVID-19 were under 45
80 years.

81 Additionally, PSC was the most common underlying disease among 28.4% and 42% of the waiting list and recipients
82 of liver transplant, respectively. Moreover, HBV, cryptogenic, hepatitis and PSC were also observed as underlying
83 disease in the waiting list and recipients of liver transplant. At present, 80% (8/10) of the COVID-19 patients have
84 recovered discharged from hospital and two patients (20%) died from respiratory failure: one patient from the waiting
85 list and one from recipients of liver transplant .The demographics and details of underlying disease are shown in Table
86 1.

87 According to results of laboratory values, patients on the waiting list with COVID-19 infection had higher median of
88 albumin (4.03 g/L), ALT (65.5 U/L), AST (51.2U/L), TBIL (1.6 mmol/L), DBIL (0.61mmol/L), HDL (66.5) and LDL
89 (95) value compared to recipients of liver transplant with COVID-19 infection. While, albumin (4.2 g/L), HDL (48.7)
90 and LDL (87.5) were relatively higher in recipients of liver transplant patients without COVID-19. Moreover, the
91 mean dose of vitamin D in patients on the waiting list without COVID-19 and transplant patients with COVID-19
92 were 35.4 ± 20.2 and 47.1 ± 6.2 , respectively and were partially higher in compared to other group .Clinical and
93 laboratory finding of recipients and patients on the waiting list for liver transplantation without and with COVID-19
94 are presented in Table 2.

95 As shown in Table 3, history of drug use in liver transplant patients infected with COVID-19 was more than patients
96 on the waiting list. The details of medication history among transplanted and patients on the waiting list for liver
97 transplantation without and with COVID-19 are shown in Table 3.

98 **Discussion**

99 Since ACE2 enzyme has a proven role in the pathogenicity of COVID-19 and due to the plentiful production of this
100 enzyme in hepatic and biliary epithelial cells, the liver is considered as a target organ for this virus (17-19).

101 The Centers for Disease Control and Prevention (CDC) has stated that patients older than 65 years, and those with
102 liver diseases are at higher risk of fatal disease (20), therefore, regarding to insufficient data on chronic liver diseases
103 and patients with liver transplantation during the COVID-19 pandemic in our region , the aim of the present study was
104 a descriptive study of the incidence and mortality rate of COVID-19 in liver transplant recipients and the patients on
105 the waiting list for liver transplantation.

106 The results of this study showed that 5.8% of patients developed COVID-19 disease, and their mortality was of 20%.

107 Regarding specifically the mortality, it remains elevated (20%) in patients with COVID-19 in our study but

108 comparable with those reported in the United states and Spain population, supporting the idea that liver transplantation
109 recipients should be considered as population at risk (21-23).

110 The incidence of COVID-19 in patients with liver transplantation especially in men over the age of 45 years was
111 higher. Moghadam et al. also reported that since patients candidate for liver transplantation experience more stress
112 before transplantation more attention should be paid (24). In this regard, Al Ghamdi et al., reported that adverse
113 outcomes in patients with liver transplantation and MERS-CoV virus were more common (25). Other results of the
114 present study showed that liver enzyme markers and bilirubin levels in patients on the waiting list for liver
115 transplantation with COVID-19 were higher. Recent studies have reported that liver injury is mainly associated with
116 abnormal ALT/AST levels and a relatively increase in bilirubin levels as well as a decrease in albumin levels in severe
117 COVID-19 cases (26, 27).

118 In addition, in a meta-analysis study, the relationship between liver damage and the severity of COVID-19 infection
119 were studied and the results showed that high serum levels of AST, ALT, total bilirubin and low serum albumin levels
120 were significantly associated with increased severity of COVID-19 (28). However, based on present study, ALT/AST
121 and albumin value were high in liver transplant patients with COVID-19. In addition, patients on the waiting
122 list for liver transplantation with COVID-19 had high level of ALT, HDL and LDL ratio than patients without COVID-
123 19.

124 According to studies, liver damage observed in patients with COVID-19 may be due to Lopinavir/ritonavi, which is
125 used as an antiviral drug to treat SARS-CoV-2 infection (29).

126 Given that liver damage can be multifactorial and heterogeneous, there is ambiguity as to whether liver damage is
127 related to underlying liver disease or due to the use of drugs prescribed to treat COVID-19.

128 PSC was the most common underlying disease in both groups of patients (30). However, HBV, cryptogenic and
129 hepatitis were also observed as underlying disease in the waiting list and recipients of liver transplant. Due to
130 transplant patients have more comorbidities than the general population, the expected severity of COVID-19 would
131 be increased (14, 31). According to the results of the present study, in general, the history of drug use was higher in
132 patients with liver transplantation. In patients with a history of drug use, the incidence of COVID-19 was higher in
133 liver transplant patients. The frequency of proton pump inhibitors and calcium D in liver transplant patients with

134 COVID-19 was higher. Moreover, in patients with COVID-19, the frequency of vitamin D intake was similar and
135 very low in both groups (32). Alqahtani et al., (2020) investigated the association of liver damage with COVID-19.
136 In their study, patients with coronavirus (COVID-19) disease experienced varying degrees of liver abnormalities. They
137 suggested treatment with acetaminophen and the avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs) in
138 cirrhosis, but caution should be exercised when using antiviral agents in patients with liver problems and drug
139 interactions after liver transplantation (27). Niknam et al. investigated two patients with COVID-19 including a 60-
140 year-old female patient with diabetes and a 46-year-old man who had previously had a liver transplant. Both patients
141 recovered after starting hydroxychloroquine and continuing to use all immunosuppressive agents except
142 mycophenolate based on the decision of the medical team with different specialties (33). However, the existence of
143 underlying liver diseases should be well known as one of the poor predictive factors for worse outcomes in patients
144 with COVID-19. So, comparative studies are recommended to identify risk factors for COVID-19 in patients with
145 liver injury (34). However, due to relatively small sample size of transplanted cases with COVID-19, our results could
146 not be completely represented the effect of immunosuppression on the course of the disease, so the analysis must be
147 interpreted caution.

148 In conclusion, the results of the present study showed that the incidence of COVID-19 in liver transplant patients was
149 slightly higher. The existence of underlying liver diseases should be well known as one of the poor predictive factors
150 for worse outcomes in patients with COVID-19. So, comparative studies are recommended to identify risk factors for
151 COVID-19 in patients with liver injury.

152 **List of abbreviations**

153 SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE2: angiotensin-converting enzyme-2; PSC:
154 primary sclerosing cholangitis; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B; AST: aspartate
155 aminotransferase; HDL: High-density lipoprotein; DBIL: direct bilirubin; TBIL: total bilirubin; CTscan: computed
156 tomography scan; SD: standard deviation; CDC: Centers for Disease Control; NSAIDs: nonsteroidal anti-
157 inflammatory drugs

158 **Ethics approval and consent to participate**

159 This study was approved by the research ethics committee of Guilan University of Medical Sciences, Rasht, Iran with
160 number code IR.GUMS.REC.1399.135. written informed consent to participate in the study was obtained from
161 participants.

162 **Consent for publication**

163 Not applicable.

164 **Availability of data and materials**

165 The datasets used and/or analyzed during the current study are available from the corresponding author on
166 reasonable request

167 **Competing interests**

168 The authors report no conflicts of interest in this work

169 **Funding**

170 Self- funding

171 **Authors' contributions**

172 Conceived and designed the experiments: PR, MSD and MTA. Performed the experiments: MNT, KM and AS.

173 Analyzed the data: MNT and KM. Contributed reagents/materials /analysis tools: RR and MH. Contributed to the
174 writing of the manuscript: MTA PR and MSD. All authors read and approved the final manuscript.

175 **Competing interests**

176 The authors report no conflicts of interest in this work

177 **Acknowledgements**

178 Not applicable

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285 **Table 1.** Baseline characteristics of study population.

Variable	Transplanted (N:87)	Before undergoing a liver transplant (N: 85)	Transplanted with COVID-19 (N:6)	Before undergoing a liver transplant with COVID-19 (N: 4)
Age	58.5±12.9	62.2±13.95	-	-
BMI	24.1±4.4	25.8±4.5		
Sex				
• Male	59(67.8)	49(57.6)	5 (83.3)	3 (75)
• Female	28(32.6)	36(42.9)	1 (16.7)	1 (25)
Clinical Outcome				
Death	1	1	1	1
Discharge	86	85	5	4
Underlying disease				
PSC	34(42)	19(28.4)	-	1 (25)
Cryptogenic	16(19.8)	9(13.4)	1 (16.7)	1 (25)
Hepatitis	9(11.1)	14(20.9)	1 (16.7)	1 (25)
Nash	3 (3.7)	13(19.4)		
HBV	8(9.9)	3(4.5)	2 (33.3)	
Other	12(13.6)	10(13.4)	2 (33.3)	1 (25)

286 BMI: body mass index; PSC: primary sclerosing cholangitis; Nash: Non-alcoholic steatohepatitis; HBV: Hepatitis B

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291 **Table 2:** Clinical, laboratory of recipients and patients on the waiting list for liver transplantation without and with
 292 COVID-19

Variable	Transplanted (N:87)	Before undergoing a liver transplant (N: 85)	Transplanted with COVID-19 (N:6)	Before undergoing a liver transplant with COVID-19 (N: 4)
Blood biochemistry				
Albumin (g/L)	4.2±0.61	3.7±.54	3.9±0.59	4.03±0.21
ALT(units /L)	26.7±24.02	45.7±26.4	46.3±38.2	65.5±43.4
AST(units /L)	24.7±17.5	53.5±32.9	29.3±13.7	51.2±16.1
TBIL (mmol/L)	0.98±0.61	4.6±1.8	0.54±0.3	1.6±0.84
DBIL	0.31±0.19	0.76±1.1	0.32±0.13	0.61±0.26
HDL	48.7±13.9	46.7±16.1	40.6±17.3	66.5±19.1
LDL	87.5±31.6	84.1±3.2	87.2±26.5	95±5.6
Vitamin D				
Vitamin D doses	33.8±18.5	35.4±20.2	47.1±6.2	41.5±24.04
Vitamin D usage (No, (%))	15 (17.2)	15 (17.6)	1 (16.7)	1 (25)

293 TBIL: Total bilirubin; DBIL: direct bilirubin; HDL: High-density lipoprotein; LDL: low-density lipoproteins

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298 **Table 3: Treatment among transplanted and patients on the waiting list for liver transplantation without and**
 299 **with COVID-19**

Variable	Transplanted (N:87)	Before undergoing a liver transplant (N: 85)	Transplanted with COVID-19 (N:6)	Before undergoing a liver transplant with COVID-19 (N: 4)
Prednisolone	64 (73.6)	17 (20)	2 (33.3)	-
Cellcept	38 (43.7)	1 (1.2)	2 (33.3)	-
Folate	52 (59.8)	23 (27)	3 (50)	-
Tacrolimus	77 (88.5)	2 (2.3)	2 (33.3)	-
Aspirin	16 (18.4)	8 (9.4)	1 (16.7)	-
Calcium	68 (78.2)	19 (22.4)	4 (66.7)	1 (25)
Multivitamin	2 (2.3)	14 (16.5)	-	1 (25)
Proton-Pump Inhibitor Drugs (Ppis)	49 (56.3)	26 (30.6)	4 (66.7)	-
Azithromycin	1(1.2)	1(1.2)	1 (16.7)	-
Hydroxychloroquine	3 (3.4)	-	2 (33.3)	-
HMG-Coa Reductase Inhibitors	10 (11.5)	17 (20)	2 (33.3)	-
Insulin	7 (8)	10 (11.8)	1 (16.7)	1 (25)
Tavanex	3 (3.4)	-	2 (33.3)	-
Metformin	10 (11.5)	6 (7)	2 (33.3)	-
Ursodeoxycholic Acid (UDCA)	41 (47.1)	28 (32.9)	2 (33.3)	1 (25)
Mesalazine	11 (12.6)	6 (7)		1 (25)

Levothyroxine	3 (3.4)	6 (7)	1 (16.7)	
Spironolactone	-	4 (4.7)	-	1 (25)
Sirolimus	1 (1.2)	-	3 (50)	
Propranolol	15 (17.2)	1(1.2)	1 (16.7)	
Losartan	5 (5.7)	5 (5.9)	1 (16.7)	
Carvedilol	-	16 (18.8)		2 (50)

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Authors' contributions

Conceived and designed the experiments: PR, MSD and MTA. Performed the experiments: MNT, KM and AS.

Analyzed the data: MNT and KM. Contributed reagents/materials /analysis tools: RR and MH. Contributed to the writing of the manuscript: MTA PR and MSD. All authors read and approved the final manuscript.

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