



Effects of COVID- 19 on Living Donor Liver Transplantation at a Leading Transplant Unit of a Third World Country

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Abstract

Background and Aims: The novel Coronavirus (COVID-19) pandemic with rapidly rising number of cases and high mortality massively affected living donor liver transplantation in Pakistan. The study aims at providing an insight into the transplantation in era of pandemic, its effects on LDLT in postoperative period.

Methods: All the patients listed for LDLT at PAQSJIMS from March 1st to June 30th 2020 were re-evaluated for LDLT, after an initial complete halt and mortality of 3, in terms of CTP, MELD, COVID PCR and CT chest, for resumption of transplantation services and were closely monitored postoperatively.

Results: 54 patients with Child C, MELD above 15 and negative PCR/HRCT underwent LDLT. 6 (5 recipients and 1 donor) out of 70 listed, tested positive on PCR, were deferred from surgery and followed. Majority of recipients were males in their forties to sixties, with normal BMI, no comorbidities, and underwent LDLT for chronic viral hepatitis with decompensated cirrhosis (HBV+ HDV, HBV, HCV) and unresectable hepatocellular carcinoma. Postoperatively 5 Recipients (no donors) were diagnosed with SARS clinically, 4 tested positive on PCR and 1 had CT findings highly suggestive of COVID infection. Mortality was 2/5, caused by MOF in patient with prolonged illness, and sudden cardiac death in a relatively well patient.

Conclusion: In conclusion, COVID 19 can have an atypical clinical presentation in postliver transplant patients, patients may be pre-symptomatic or asymptomatic and can have cardiac arrhythmias. Symptomatic patients may not necessarily have Positive PCRs, HRCT findings should be considered in all symptomatic patients, before labelling them COVID negative based on PCR. Strictly following SOPs can reduce transmission of COVID-19.

Keywords: Coronavirus (COVID-19); Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2); Liver Transplantation

Introduction

Coronavirus (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 30.6 million individuals, and caused 950,000 deaths globally. There have been 305671 cumulative cases with 6416 deaths in Pakistan by September 20th 2020 [1]. The First case of COVID-19 was confirmed by the Ministry of Health, government of Pakistan on February 26, 2020 in Karachi, Sindh province [2] and was followed by a massive increase in case numbers and mortality in Pakistan like several countries of the world. Due to novelty of the virus, the baseline data was almost non-existent, and the research in beginning of the outbreak, in forms of case reports or short case series, focused on its pathogenicity and severity of disease. More recent publications provide a better understanding of the clinical manifestations, course and severity of disease, and morbidity and mortality, in both general population and population at higher risk. However, the data on the effects of disease on Liver transplant recipients in the relatively vulnerable early postoperative period, and transplant candidates on waiting list is scarce.

Purpose of the Study

The purpose of this study is to provide an insight on the living donor liver transplantation amidst pandemic, its effects on LDLT patients in postoperative period, and on waiting list.

Materials and Methods

All patients who were listed for Living donor Liver transplantation at PAQSJIMS from March 1st to June 30th 2020 were enrolled for a prospective longitudinal study after obtaining written informed consent from all patients and approval from Research and ethical board of the institute. A baseline demographic and detailed clinical data was collected from both donor and recipients.

Living Donor liver transplantations at PAQSJIMS were initially halted for three weeks due to rapidly rising numbers of cases of the novel viral pandemic. But an increase in mortality amongst the patients (16%) on waiting list, more than the baseline mortality of 7% prompted resumption of services after extensive measures, since PAQSJIMS is the only Transplant unit in public sector with high volume of cases. All the cases listed during the given time period were re-assessed in terms of short-term prognosis, disease severity (CTP) and urgency of transplantation (MELD and UNOS). Cases with worsening clinical condition, Child C or MELD >15, Hepatocellular carcinoma and UNOS 2B or higher proceeded for transplant. All the relisted Recipients and their Donors underwent Universal screening for COVID-19 reverse transcriptase-polymerase chain reaction of a nasopharyngeal swab test, regardless of the epidemiological risk or clinical picture. All the recipients or donors tested positive on PCR before intended date of surgery were deferred from Transplantation. The tests were repeated on Day 7, and if positive repeat tests were taken on day 21, and every 6 weeks until negative. Deferral period was kept 6 weeks to rule out potential outliers. Recipients and donor tested negative underwent further evaluation for COVID 19 clinically and with imaging (chest x-ray and HRCT). Those with normal chest x-ray and HRCT chest proceeded for transplantation.

All members of Liver transplant team, theatre staff, ICU staff underwent screening for COVID-19 PCR. Only those tested negatives and asymptomatic were involved in patient care. All standard theatre and ICU protocols were followed during and after surgery. Postoperatively the recipients with respiratory complications or prolonged ventilation requirements, deterioration not related to Liver transplantation, or chest x-ray findings suggestive COVID infection were retested for COVID 19. They were isolated with strict measures to prevent patient to patient or patient to healthcare professional spread of suspected infection until proven otherwise.

They were assessed for clinical manifestations of COVID-19, Laboratory results, imaging, modification in immunosuppression, and outcome in terms of need for ventilator or oxygen support, days of hospitalization and mortality. All the discharged recipient and donor were followed for a minimum 6 weeks.

Statistical analysis was carried out by using SPSS (v.22; IBM). Descriptive statistics were calculated as means and SD for continuous and proportions for categorical variables. t test was used for continuous data, and the chi-square test was used for categorical data. P < 0.05 was considered statistically significant.

Results

82 patients were listed for Living donor Liver transplantation at PAQSJIMS in the period under review. Upon re-evaluation, 6 tested positive (5 recipients and 1 donor) for COVID 19 on PCR (nasopharyngeal swab test). LDLTs in PCR positive patients regardless of the symptoms were deferred until the tests were negative and patients asymptomatic; they are currently being followed. 64 LDLTs were done. There were 54 males and 10 female recipients. Majority of the recipients were in forties to sixties 57.8% (n = 37), followed by twenties 17.2% (n = 11) and thirties 17.2% (n = 11) age bracket, while only two patients were under 20 years of age. 57.8% (n = 12) patients had normal BMI, 18.7 % (n = 12) were overweight, 9.4 % (n = 6) obese, while 14.1% (n= 9) were undernourished. Majority of donors were male (70.3%), in twenties (60.9%) and had normal BMI (65.6%). The most common indication for liver transplantation was chronic hepatitis with decompensated cirrhosis, due to HBV+ HDV in 26.6% (n = 17), HBV in 23.4% (n = 15) and HCV 12 (n = 18.8%), followed by unresectable hepatocellular carcinoma in 15.6% (n = 10), while only 2(3.1%) patients underwent LDLT due to Buddchiari Syndrome and 1(1.6%) for AIH. Around 67.2%(n = 43) patients were Child C, 26.6% (n = 17) Child B, while only 6.3% (n = 4) patients were CTP A. A total of 95.3% (n = 61) had MELD score above 10. Recipient and donor demographic characteristics are shown in table 1-4.

Despite screening and adequate measures to prevent and control SARS-CoV-2 infection, two discharged and four inpatients developed symptoms suggestive of COVID 19. All were Recipients, 5 males and 1 female. Out of six, five tested positive on PCR. One of the two discharged patients (patient 1) was readmitted with Cholangitis from post-transplant clinic on his third follow up visit. He was a 43 years old male, with no clinical features consistent with COVID -19 infection, except for a fever. He tested Positive for COVID 19 on PCR, had normal imaging, and did not require any additional treatment. He was medically released after 14 days of hospitalization for Cholangitis. He later underwent PTBD followed by ERCP and stenting for Biliary stricture on outpatient basis and had negative Covid-19 PCRs before both procedures.

Patient 2, a 56 years old lady presented 5 days after discharge from hospital, with sudden onset of severe shortness of breath and hypotension, that rapidly progressed to severe respiratory distress, shock and multiorgan failure. Her HRCT demonstrated more than 50% multilobar bilateral lungs involvement with architectural distortion and bronchiectasis. Her PCRs remained consistently positive, and she showed no improvement in clinical and laboratory parameters despite maximal treatment and eventually passed away after 45 days of ICU care.

Contrary to the severe prolonged illness or Pneumonias leading to death in patients with COVID 19 infection, three of the four in-patients in current study developed mild shortness of breath, fever with malaise, while one developed self-resolving diarrhoea for a day. They had mild derangements in liver function tests, and three of them tested positive on COVID 19 PCR, while one tested negative. None of the patients required additional treatment. However, the immunosuppression with CNI was temporarily withheld in all three. One of these PCR positive patients (Patient 5) a 37 years old male—otherwise well with mild symptoms, and mild right pleural effusion on chest Xray—was being discharged on 9th postoperative day to continue his quarantine and the rest of his treatment at home. Minutes before leaving, he developed severe arrhythmia and could not be saved despite resuscitation.

While the 6th patient was a 58 years old male patient with worsening respiratory parameters and increasing oxygen requirements. He tested negative for COVID -19 on PCR. However, his CT findings of bilateral ground glass appearance of lung, peripheral opacities and bilateral Pleural effusion were consistent with COVID 19 Pneumonia. Nonetheless he was kept in isolation and managed as COVID positive patient. He showed substantial improvement in clinical parameters and CT findings, while his PCR remained negative on repeated testing. He was medically released after 24 days of hospitalization.

Discussion

The coronavirus COVID-19 pandemic is an ongoing global health crisis that has spread to all continents of the world except Antarctica [3]. Though the transplant society consider liver and kidney transplants as safe procedures during COVID-19 pandemic [4], the liver transplant recipients are at increased risk of acquiring COVID 19 infection, high viral loads, and severe clinical manifestation due to use of immunosuppression [5]. Other proposed risk factors like old age, male sex and presence of comorbidities, may potentiate disease progression and cause death by sequential organ failure [6]. However, in current study, only 2 COVID 19 confirmed Liver transplant recipients were above 50 years of age, and none of the five COVID 19 PCR positive patients had coexisting diseases, which is quite contrary to the published data on general population.

The clinical manifestations of COVID 19 infection are atypical, and may range in severity from subclinical anosmia, to severe prolonged potentially life-threatening Pneumonias, respiratory failure, sepsis shock, multiorgan failure [1,7-9] or bizarre fatal cardiac arrhythmias [10,11] in relatively well patients with no plausible cause of arrhythmia or coexisting cardiac disease. COVID 19 infection have also been documented in patients who are either asymptomatic or have not yet developed symptoms. These pre-symptomatic patients may have radiological findings (on chest Xray) before onset of symptoms [12,13], and can shed virus and transmit disease [14,15]. In current study, four PCR confirmed COVID 19 infected pre-transplant candidates were asymptomatic, while a Recipient donor pair, brother and sister had mild symptoms of anosmia and flu. None of the listed patients required hospitalization, or oxygen supplementation, they remained suspended from list until PCR was negative. Three of the five PCR confirmed Post liver transplant recipients became symptomatic in the immediate post-operative period. They had mild right pleural effusion on imaging, which is commonly observed in liver transplant recipients and cannot be totally attributed to COVID 19. They had milder form of infection, like most of the general population [1,16-18] that resolved without additional treatment.

In current study, a female patient (patient 2) readmitted after an uneventful discharge from hospital developed severe COVID 19 infection, that eventually proved fatal despite maximal ICU care of 45 days. Her clinical presentation with prolonged ventilator requirements and persistently positive PCRs were typical of the life-threatening COVID 19 positive patients seen globally [19,20]. A similar presentation was observed in a male liver transplant recipient with comparable age and other clinical parameters. His severe shortness of breath requiring continuous oxygen support, fever and persistent hypotension necessitating low dose inotropic support, were consistent with moderate to severe COVID 19 infection. His CT images depicting bilateral ground glass appearance of lung, peripheral mixed opacities, and bilateral Pleural effusion were characteristic of SARS-COV2 Pneumonia. However, his first and subsequent PCR swab were all negative. This is identical to a case reported by Feng H [21], which raised questions at accuracy of diagnostic methods. Although PCRs of the respiratory tract samples are considered gold standards for identification and laboratory confirmation of COVID 19, and have been recommended by WHO [22] and CDC [23] for diagnosis of COVID 19 in clinical settings, the sensitivity of PCR (83.3%) is lower than the sensitivity of an initial CT (97.2%) [24] in diagnosis of COVID 19. Furthermore, a meta-analysis on chest CT versus RT-PCR for diagnostic accuracy of COVID-19 [25] depicted initial CT to be more rapid and cost effective than RT-PCR in the detection of COVID-19 in hospitalized patients. Nonetheless the patient in current study was considered and managed as COVID positive based on clinical findings and imaging.

Contrary to the severe respiratory failure or MODS as dominant cause of death in COVID cases, a young male patient in current study without any underlying cardiovascular disease or comorbidities, had sudden cardiac death due to an arrhythmia. There have been isolated case reports on sudden cardiac deaths in COVID positive patients without preexisting cardiac conditions. Albeit, various multinational studies, have identified cardiovascular disease as an independent risk factor for an increased in-hospital death in COVID positive patients [26].

Since its emergence in late 2019, efforts have been made to estimate the impact of pandemic in terms of outcome, which is predicted to be greater than indicated by official data. The COVID 19 mortality estimation by calculation of case fatality ratios have been misleading worldwide [27], due to variations in clinical presentation, number of actual cases, missed cases, herd immunity, serological testing strategies, quality of care, and patient profile. In current study, amongst a total of 6 pretransplant (5 Recipients and 1 potential donor) and 5 post-transplant patients (recipients) with positive PCRs, mortality was two.

Limitations to Study

Our study has several limitations, Firstly, lack of data especially on pretransplant candidates, due to incomplete documentation of the COVID 19 exposure history and laboratory testing; urgent timeline for data collection; variable incubation period, and recall bias. Secondly, the retro prospective study required day to day modification in management strategies with updates on information, due to novelty of virus. Thirdly, the data generation was clinically driven and not systematic. Fourthly, short sample size, a larger sample size over a larger timespan could provide better understanding of the disease burden in the Liver transplant candidates.

Conclusion and Recommendations

In conclusion, COVID 19 can have an atypical clinical presentation in postliver transplant patients, OR patients may be pre-symptomatic or asymptomatic. Symptomatic patients may not necessarily have Positive PCRs, HRCT findings should be considered in all symptomatic patients, before labelling them COVID negative based on PCR only. COVID 19 should be considered in differentials of unexplained life-threatening Arrhythmias in Post liver transplant patients without pre-existing cardiac disease. Hospital acquired COVID-19 related infection rates and mortality in post liver transplant patients can be effectively reduced by increasing patient centered care, isolating all suspected cases, periodically testing all health care staff involved in patient care, and following Hospital SOPS of infection prevention and control i.e. mask gowns, handwashing/sanitization, to prevent transmission. Single Visitor policy can be implemented, and Visitors should be tested for COVID 19.

Table 1: Demographics of Recipient and Donor Pairs who underwent LDLT (n=64)

Characteristics	Recipients (n=64)		Donors (n=64)	
	Number	Percentage	Number	Percentage
Age				
< 20	3	4.7%	14	21.9%
21 - 30	11	17.2%	39	60.9%
31 - 40	11	17.2%	11	17.2%
41 - 50	19	29.7%	--	--
51 - 60	18	28.1%	--	--
> 60	2	3.1%	--	--
Sex				
Male	54	84.4%	45	70.3%
Female	10	15.6%	19	29.7%
BMI				
< 18.4	9	14.1%	14	21.9%
18.5 - 24.9	37	57.8%	42	65.6%
25 - 29.9	12	18.7%	8	12.5%
30 - 34.9	6	9.4%	0	0
Blood group				
O	25	39.1%	37	57.8%
A	11	17.1 %	7	10.9%
B	24	37.5%	17	26.6%
AB	4	6.3%	3	4.7%

Table 2: Recipient Preoperative Clinical Parameters, indications for LDLT and Postoperative complications (n=64)

MELD	Number of patients	Percentage
< 9	5	7.8%
10 - 19	31	48.4%
20 - 29	27	42.2%
30 - 39	1	1.5 %
CTP		
A	4	6.2%
B	17	26.6%
C	43	67.2%
Comorbidities		
DM	7	10.9%
HTN	3	4.6%
COPD	1	1.5%
Obesity	18	28.1%

Indication		
HBV -HDV	17	26.6%
HBV	15	23.4%
HCV	12	18.8%
HCC	10 (HBV induced 1+ HCV induced)	15.6%
BCS	2	3.1%
AIH	1	1.6%
Others	7	10.9%
Complications		
Right Pleural effusion	62(mild)	96.9%
	2 (moderate to severe requiring intervention)	3.1%
Vascular Complications: (HAT requiring urgent re-exploration)	1	1.6%
Biliary complications	2 (required surgical intervention)	3.1 %
Outcome		
COVID PCR Positive	5	7.8 % of total Transplant patients
Prolonged hospital stay	3	4.7%
Mortality due to COVID	2	3.1%

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Table 3: Demographics, Clinical Parameters, modification in immunosuppression and outcome in PCR positive Post liver transplant patients (n = 5)

Patient characteristics	Number	
Age		
31-40	2	40%
41-50	1	20%
51-60	2	40%
Sex		
Male	4	80%
Female	1	20%
Disease symptoms		
Fever	2	40%
chills	1	20 %
Malaise	2	40%
Cough	1	20 %

SOB	4	80%
Diarrhoea	1	20%
Disease severity (n = 5)		
Mild	2	40%
Moderate	2	40%
Severe	1	20%
Modification in Immunosuppression		
Decrease or Hold Steroids	1	20%
Decrease or Hold CNI	4	80%
Outcome		
Prolonged hospital stay	2	40%
Mortality due to COVID-19	2	3% of total Transplant patients (n = 65)

Table 4: Radiological findings consistent with COVID 19 (COVID PCR positive = 5, COVID PCR negative = 1).

Pleural effusion mild	3	50% (covid patients)
Bilateral mixed ground glass appearance involving nearly 25% of lungs, and bilateral Pleural effusion	1	16.6%
> 50% multilobar bilateral lungs involvement with architectural distortion and bronchiectasis, bilateral Pleural effusion	1	16.6%

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