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ORIGINAL ARTICLE

Single Center Analysis of Incidence and Outcome of COVID-19 Infection in Solid Organ Transplant Recipients Treated at Bahria International Hospital, Lahore, Pakistan

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ABSTRACT

Aim: To determine overall mortality, outcome and mortality of COVID 19 infection in solid organ transplant pts.

Study design: Retrospective study.

Place and duration of study: Department of Medicine, Bahria International Hospital, Lahore, Pakistan15th April 2020 to 31stDecember 2020.

Methodology: Twenty-three patients 18 out of which were kidney transplant recipients while 5 were liver transplant recipients. All the solid organ transplant patients who were admitted with Sars CoV2 (Corona virus) infection were recorded. Their charts were reviewed regarding clinical course, management, and outcome of COVID-19 infection in recipients of solid organ (liver and kidney) transplant.

Results: Mean age was 44.8±10.9 years. Median time lapsed from transplant surgery to admission was 2.88 years (interquartile range 2.25, 7.33). Median hospital stay was 15 days (interquartile range 13, 28). All 23 patients were admitted and managed, with 17 (73.91%) admitted in ICU. Over half of the cases (58.2%) presented with raised serum creatinine due to acute kidney injury. 80% received azithromycin, Tocilizumab and 50% received Remdesivir.Antimetabolites with or without calcineurin inhibitors were held or reduced. A total of 5 patients had died while the others 18 patients (78.26%) were discharged home.

Conclusion: There is a theoretical high risk of getting Sars CoV-2 infection in post-transplant patients but we did not find any increase in overall mortality in solid organ transplant recipients receiving immunosuppressive therapy who acquired Sars CoV2 infection as compared with mortality in the general patients with SARS-CoV-2. We had favorable outcome in solid organ transplant COVID 19 patients in our center.

Keywords: Incidence, Outcome, COVID-19, Infection

INTRODUCTION

The novel coronavirus SARS-CoV-2 (COVID-19)] has taken the world by a storm. Although most cases with COVID-19 have mild-to-moderate symptoms but vulnerable patients for example those with older age and having medical conditions like Diabetes, Hypertension, Ischemic heart disease, chronic obstructive lung disease (COPD), end stage renal disease (ESRD), immunocompromised exhibit severe COVID-19 disease.[1,2]

It is a general approach that solid organ transplant recipients are at increased risk to get infected with Sars Co-V-2 (Corona virus also known as COVID-19) because they are immunosuppressed and have frequently come in contact with the health care personnel. Since the outbreak of COVID-19 and its spread as pandemic there has been emerging literature describing the clinical features and general outcome of Sars Co V 2 infection in post-transplant cases[1].

A lot has been focused on the process of transplantation itself in the COVID era from organ retrieval to harvesting with regard to creating and managing a set up related to transplantation with strict isolation and infection control[2-4].

Keeping one's index of suspicion wide enough to pick Sars Co-V-2 infection in this large and special pool of patients is especially important as the clinical features may vary from the immunocompetent patients fever for example is less common, possibly due to the effects of immunosuppressant medicines on the systemic inflammatory response. Similarly, Lymphopenia may be more prominent in solid organ transplant patients than in nontransplant cases with COVID-19.[5,6]

Detailed evaluation of clinical symptoms of disease and progression, with the help of biomarkers are important for appropriate handling and treatment of COVID-19 positive solid organ transplant recipients. The evidence about effects and outcomes of COVID-19 on the liver and kidney transplant organ systems is surfacing slowly in current literature. Herein, we present our experience with 23 solid organ recipients who were diagnosed with Sars co-V-2 infections and admitted for treatment.

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MATERIALS AND METHODS

A retrospective charts analysis of all the solid organ transplant patients admitted with COVID-19 infection from 15thApril 2020 to 31stDecember 2020.Bahria International Hospital is a transplant center for Liver and Kidney transplant. It is 4th largest center in country and second largest in private corporate sector. We have completed more than 200 Kidney transplants and more than 40 liver transplants so far since 2018.All data was collected retrospectively. We reviewed patients' demographics including age and gender, clinical presentation, body mass index (BMI), comorbidities, type of organ transplanted, time-lapsed from transplantation to COVID-19 infection, immunosuppression, laboratory findings like complete blood count (CBC), liver function tests (LFTs), serum creatinine (Cr), IL-6, CRP, D-Dimers, LDH, Ferritin and imaging including Chest X-rays and High resolution Computerized Tomographic Scan (HRCT). Their clinical course, concomitant infections, treatment modalities and outcomes were also reviewed.

Bahria International Hospital, Lahore has an established COVID-19 treatment protocol created by a hospital-based multidisciplinary team (MDT) in order to standardize the management and prioritize potential research studies for COVID-19 positive patients at our place. The standard protocol divides the patientsinto three groups (mild, moderate and severe)depending on severity of symptoms. Moderate symptoms are fever, cough/SOB and 1 of the following: age ≥65 years old, presence of diabetes mellitus (DM), coronary artery disease, obesity (BMI > 30), LDH > 3 times normal. Severe symptoms were defined as having 1 of the following: tachypnea (respiratory rate > 30 breaths/min), hypoxia (SpO_2 < 94% on room air), respiratory failure, and/or need for ICU admission due to intubation status.

All cases were given Azithromycin except those with long QTc interval greater than 450ms, and dosed at 250 mg twice a day. A Cytokines release syndrome (CRS) criterion is used at our institution for monitoring and administration of Tocilizumab. Steroids were standard to 40 mg prednisolone twice a day or equivalent doses of dexamethasone. Supportive therapy and additional antibiotics were used as per protocol. The immunosuppression was adjusted daily by MDT. The MDT comprises of transplant surgeons, transplant nephrologists, transplant hepatologists, infectious disease and intensive care consultants. All COID-19 patients admitted to ICU were also managed by the same team.

Immunosuppression was managed by holding antimetabolite mycophenolate mofetil (MMF) or azathioprine with dose adjustment of calcineurin inhibitors such as tacrolimus or cyclosporine. Tacrolimus was adjusted to maintain a trough level of 3–7 ng/mL as per hospital protocol. The data was entered and analyzed through SPSS-20.

RESULTS

Eighteen (78.26%) were post kidney transplant while 5 (21.73%) were post liver transplant. Our center does perform multiorgan transplant. All of them (23/23 i.e., 100%) were tested positive by PCR and all of them were admitted for observation and management. Post-transplant COVID-19 cases had an average age of 44.8±10.9 years when admitted. Seven patients were older than 65 years, wherethe oldest was 74 years old. 16/23 (69.56%) of the COVID-19 infected solid organ transplant recipients were male. The average calculated BMI was 27.8±5.4kg/m2. The median time-lapsed from transplant was 2.88 years (IQR 2.35, 7.36). Majority of them had at least 1 co-morbidity with hypertension at the top 19/23 (82.23%) stroke was least common 1/23 (4.34%) [Table 1]. More than 80% of our cases were on three immunosuppressive medications at the time of admission including Tacrolimus, Mycophenolate mofetil and prednisolone.

Out of all 23 cases majority had chills and fever as starting symptoms and more than half of them (69.56%) complained of having metallic taste in mouth (dysgeusia) loss of sense of smell was reported by 82% of them. Majority of them > 80% were admitted as the presenting symptom was indication respiratory involvement (Table 2) High resolution CT chest (HRCT) was done for all of them and21/23 (91.30%) showed finding on admission CT. Those with extensive involvement 5/23 (21.73%) required ventilatory support in ICU and none of them survived. All of them died because of severe refractory respiratory failure, septic shock and multi-organ failure due to secondary infections (Table 3)

Table 1: Demographic data of solid organ transplant patients with COVID-19 infection (n=23)

Variable	No.	%
Gender		
Male	16	69.56
Female	7	30.43
Age (years)	44.8±10.9	
BMI (kg/m^2)	27.8±5.4	
Co-morbidities		
Hypertension	19	82.23
Diabetes	13	56.52
Bronchial asthma	10	43.47
Ischemic heart disease	9	39.13
Stroke	1	4.34
Transplant Type		
Kidney	18	78.26
Liver	5	21.73
Immunosuppression		
Tacrolimus	23	100.0
Mycophenolate Mofetil	20	86.95
Azathioprine	18	78.26
Steroids (prednisolone)	18	78.26

Ten cases were treated in ICU out of which 7 were invasively ventilated 3 were managed with non-invasive ventilation. Two out of invasively ventilated cases were successfully extubated while the other five went into multi organ failure and expired. 11/23 (47.82%) were managed in HDU as they required high flow Oxygen given through high flow nasal cannula (HFNC). Two patients required less than 8 liters per minute of Oxygen and they were treated in isolation rooms. 14 cases (60.86%) developed secondary infections out of which 3/23 (13.04%) had multiple bacterial growth and one had aspergillus infection (Table 3). The median WBC count on admission was 5.4 (IQR 3.9, 9.7; range 2.3–14.7 while median absolute lymphocyte count of 534.6 (IQR 334, 855; range 233–1942) [Table 4].

Table 2: Clinical presentation and radiological findings of solid organ transplant recipients with COVID-19 infection (n=23)

Variable	No.	%
General Symptoms		
Fever	21	91.30
Chills	18	78.26
Fatigue	23	100.0
Dysgeusia	16	69.56
Dysosmia	19	82.60
Respiratory Symptoms		
Cough	19	82.60
Shortness of breath/dyspnea	20/	86.95
GI symptoms	4	17.39
Abdominal pain	3	13.04
Diarrhea	3	13.04
Nausea & vomiting	2	8.69
Radiological findings on admission		
Bilateral peripheral ground glass opacities	13	56.52
Unilateral involvement of lungs	3	13.04
Massive infiltrates bilaterally*	5	21.73
No radiological finding	2	8.69

*All these cases succumbed to respiratory and multiorgan failure

Table 3: Clinical course, presence of co-infections, treatment and outcomes

Variable	No.	%
Hospital admission	23	100.0)
ICU admission	10	43.47
Invasive Mechanical Ventilation	7	30.43
Non-invasive ventilation	3	13.04
High Dependency Unit stay	11	47.82
High flow Oxygen (HFNC)	11	47.82
Managed in ward	2	8.69
Co-infections encountered	14/23 (60.86%)	60.86
Single gram-negative bacterial growth	11	47.82
Two or more bacterial growth	3	13.04
Fungal growth (Aspergillus)	1	4.34
Discharged home	18	78.26
Died	5	21.73
Median hospital length of stay (days, IQR)	18 (8, 19)	18 (8, 19)
Median ICU length of stay (days, IQR)	7 (5, 11)	7 (5, 11)

Table 4: Pertinent laboratory findings

White cell count ×1000/µL	5.4 (IQR 3.9, 9.7; range 2.3–14.7
Absolute lymphocyte count, cells/mm3	534.6 (IQR 334, 855; range 233–1942)
C-reactive protein, mg/dL	31.8 (IQR 5.2, 43.2; range 10.0–>50)
D-dimers, µg/mL	1.57 (IQR 0.56, 2.88; range 0.57–9.72)
IL-6, pg/mL	41 (IQR 7,71.5; range 23–1089)
Lactate dehydrogenase, U/L	273 (IQR 230, 361; range 110–490)
Serum creatinine, mg/dL	2.8 (IQR 1.13, 3.28; range 0.77–7.98)
ALT IU/L	56 (IQR 29, 122; range 22- 210)

Median CRP recorded has been 31.8 (IQR 5.2, 43.2; range 10.0–>50). This finding was different from other non-transplant cases where CRP was found spiking above 300 in some patients probably due to the immunosuppression our recipient cases were already taking. Median value of D-dimer was 1.57 (IQR 0.56, 2.88; range 0.57–9.72). Interleukin 6 (IL-6) ranged from 41 (IQR 7,71.5; range 23-1089). Interestingly most of the cases had normal LFTs. Only 9 out of 23 had raised LFTs with ALT 56 (IQR 29, 122; range 22-210). Majority of our renal transplant patients 13/18 (72.22%) had raised Creatinine levels 2.8mg/dl (IQR 1.13, 3.28; range 0.77-7.98)indicating acute kidney injury(as per KDIGO guidelines).18/23 (78.26%) were discharged home while we have experienced mortality in 5/23 (21.73%) of total admitted cases. All of them were renal transplant cases and late presentation with refractory respiratory failure has been thought to be the most important factor leading to mortality. For those who were discharged the median length of stay (LOS) had been 18 (IQR 8, 19). For ICU cases median LOS had been 7 days (IQR 5, 11)

DISCUSSION

The impact of solid organ transplantation on disease severity or outcome is difficult to assess as it is unclear if solid organ transplant recipients have a higher risk of severe disease when compared to nontransplant patients. However, our study of solid organ transplant patients showed comparable mortality to non-transplant patients.

Although some studies have pointed out higher morbidity and mortality in solid organ transplant recipients [6-9] others like Molnar et al[10] found similar incidence of mechanical ventilation, acute respiratory distress syndrome (ARDS), circulatory failure and need of vasopressors, and death between transplant and non- transplant patients' groups. Another study found that despite higher risk profile, solid organ transplant recipients improved rapidly and their disease severity declined at a faster rate than others.[11]

The pathogenesis of COVID-19 is thought to comprise an interplay between direct virus induced injury and the host response, with evidence suggesting that a dysregulated and hyperintense immune response mediates more severe disease.[12] As we know that immunosuppressive agents modulate different aspects of the host immune response, the severity of COVID-19 disease could potentially be affected by the type, combinations, and dosages of immunosuppression being used. Some medications can either directly (for example, lymphocyte-depleting antibodies) or indirectly (for instance, antimetabolites) cause drop in lymphocyte count (lymphopenia), which on the other hand has been reported as an indicator for severe COVID-19 disease. Similarly, mammalian [mechanistic] target of rapamycin [mTOR] inhibitors, mycophenolate theoretically impairs host ability to mount an adequate immune response to natural infection. More interesting but converse fact is that some data suggests that mTOR inhibitors may have some biological activity against SARS-CoV-2.[13] More robust data is needed to understand the impact of specific immunosuppressive agents used in transplant patients on the course of COVID-19 disease.

With the aforementioned facts clinicians treating COVID 19 should have a wider index of suspicion when dealing with solid organ transplant patients in order to timely diagnose and intervene Sars Co-V-2 infection.

While considering the management of solid organ transplant patients with Sars Co-V-2 infection the optimal approach has not yet beendefined, our practice at Bahria International Hospital is that we usually reduce immunosuppression in patients with moderate to severe COVID-19 disease. There is a full panel consisting of transplant surgeons, transplant physicians, intensivists, infectious disease consultants who take the decision to reduce immunosuppression and is carefully weighed against the risk for acute rejection, particularly in transplant recipients who generally require high levels of maintenance

immunosuppression.Data supporting our approach is limited to observational studies.[14-17]

We usually hold the antimetabolite mycophenolate mofetil, especially in cases who have lymphopenia i.e. absolute lymphocyte count <700 cells/mL, while the calcineurin inhibitors (CNIs) is continued as CNIs inhibit interleukin (IL) 6 and IL-1 pathways to help alleviate the development of the severe, dysregulated immune response also known as Cytokines Release Syndrome seen in some patients with severe COVID-19.[18] All cases received glucocorticoids as per protocol due to respiratory involvement majority were given dexamethasone 19/23 while4 received methylprednisolone. Only 15 cases received anti-viral drug Remdesivir as it was not available in Pakistan in the initial days of the first wave. 20 cases were given Tocilizumab when they fulfilled criteria of Cytokines release syndrome. Regarding antibiotics all were started on Azithromycin as per protocol and the antibiotics were escalated in those who showed signs of secondary infection after appropriate assessment and review by infectious disease consultant.

Our focus from the start of pandemic had been clear regarding the transplant cases and a clear protocol has been designed to asses and diagnose COVID19 disease in with a low threshold to admit them if needed. Over all we have good outcome and this can be attributed of having an established system and guidelines to tackle such difficult cases.

CONCLUSION

Although the data regarding COVID-19 infection in post-transplant patients is emerging it is clear that the centers taking care of such cases should have high index of suspicion to test and detect Sars Co-V-2 infection as early diagnosis is the key to a successful outcome. Late presentation with respiratory involvement usually has grim prognosis. Establishing institutional guidelines and formulating a multi-disciplinary team to manage such cases is recommended.

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