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ABSTRACT

BACKGROUND: The epidemiological and clinical characteristics of heart transplant (HTx) recipients during the SARS-CoV-2 epidemic remains unclear. We studied the characteristics of HTx recipients during Dec 20, 2019 and Feb 25, 2020 in an effort to understand their risk and outcomes.

METHODS: All accessible HTx recipients were included in this single-center, retrospective study. We collected information on the recipients using a web-based questionnaire as well as the hospital database.

RESULTS: We followed 87 HTx recipients (72.4% were men and average age was 51 years). 79 recipients resided in Hubei, and 57 recipients had a Wuhan related history of travel or contact. The majority took precautionary measures while in contact with suspicious crowds. 96.6% of the families and communities undertook prevention and quarantine procedures. 4 upper airway infection were reported, and 3 of them tested negative for SARS-CoV-2 (the 4th recovered and was not tested). All cases were mild and successfully recovered after proper treatment. Laboratory results of 47 HTx cases within the last 2 months were extracted. 21.3% recipients had pre-existing lymphopenia and 87.2% of recipients had therapeutic tacrolimus concentration (5-12ng/ml). 5 and 6 recipients had liver and kidney insufficiency respectively.

CONCLUSION: HTx recipients that practiced appropriate prevention measures had a low rate of infection with SARS-CoV-2 and transition to COVID-19. These early data will require confirmation as the pandemic establishes around the world.

KEY WORDS: heart transplantation, COVID-19, SARS-CoV-2, angiotensin converting enzyme 2, immunosuppressive therapy

INTRODUCTION

Since December, 2019, a kind of novel coronavirus infection later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by International Committee on Taxonomy of Viruses (ICTV) broke out in Wuhan, Hubei, PRC.[1-3] The virus targets airway epithelium using angiotensin converting enzyme 2 (ACE2) as a receptor and causes a novel coronavirus related pneumonia (NCP). Some severe cases develop into acute respiratory distress syndrome (ARDS), which can be fatal.[4] The infection spread throughout China and all over the world within 2 months. As of Feb 25th, 2020, report from world health organization (WHO) indicated a total of 81,109 lab confirmed cases, from 38 countries and regions. Of them China had more than 78000 cases, and deaths had exceeded 2700.[5]

Current epidemic evidence suggested the SARS-CoV-2 was highly contagious and humans were generally susceptible.[6] While most of the cases were mild or moderate and recovered after proper treatment, patients with underlying morbidities carried a substantial higher mortality than those without, especially those with cardiovascular disease. Also, severe cases can develop complications other than respiratory syndromes, and reports suggest 7-12% of the patients experience acute cardiac damage.[2, 7]

Solid organ transplantation (SOT) recipients including heart transplant (HTx) recipients have a higher infection risk compared to the normal population due to immunosuppression by anti-rejection therapy.[8,9] However, epidemiological and clinical characteristics of HTx recipients during the SARS-CoV-2 epidemics is largely unknown so far. We designed a

comprehensive questionnaire to collect exposure history, clinical manifestations and treatments of HTx recipients in our hospital.

METHODS

All patients receiving an allograft heart transplantation and discharged between July, 2015 to Jan, 2020 in our hospital were included in this retrospective, single-center study and numbered as No.1 to No.87 by date of transplantation. We obtained personal information, transplantation related history, epidemiological history, clinical manifestations and treatments through a web-based comprehensive questionnaire designed by clinical physicians and public health experts. The missing or unclear data collected from the questionnaire were reconciled by direct communication with the patients or their close relatives. Latest laboratory data of the recipients within the last 2 months were extracted from the hospital database. All data were finally checked and confirmed by two independent investigators. This study was approved by Renmin Hospital of Wuhan University Ethics Committee. Our study complies with the International Society for Heart and Lung Transplantation (ISHLT) ethics statement.

Continuous variables were expressed as mean (SD) if they were normally distributed or median (IQR) if they were not. Categorical variables were expressed as count and frequency. All statistical analyses were performed using the SPSS software, version 26.0.

RESULTS

Demographic data: A total of 87 recipients were included in the study and carefully followed-up (Table 1). There are 63 men and 24 women, average age is 51±12 years, 80 (92.0%) of them lived together with relatives, the number of relatives ranged from 1 to 8. 83 (95.4%) recipients followed the predefined anti-rejection therapy, and there was no rejection

episode in the recent 2 months, while 2 cases was admitted to hospital due to bacterial infection and subsequently discharged after proper antibiotic treatment. The accompanying comorbidities in this group include: hypertension 28 cases (32.2%), hyperlipidemia 15 cases (17.2%), diabetes 20 cases (23.0%), new onset coronary heart disease 1 case (1.1%), chronic obstructive pulmonary disease 1 case (1.1%), cerebral vascular disease 6 cases (6.9%), chronic renal dysfunction 8 cases (12.6%), gout 6 cases (6.9%), hypothyroidism 1 case (1.1%), all the recipients with comorbidities were prescribed with corresponding drugs by specifically trained physicians.

Epidemiological and exposure history: 79 recipients lived in Hubei province, while 57 recipients had a Wuhan contact related history. The whole group reported no obvious contact with confirmed or suspected Coronavirus Disease 2019 (COVID-19) patients. 11(68.8%) of 16 recipients who were in contact with asymptomatic individuals who travelled to or came back from Wuhan, had protective procedures initiated. After Jan 23 2020, 84 (96.6%) of 87 recipients undertook precautionary procedure in their community. 56 (64.4%) of 87 recipients self-quarantined at home by more than 1 week. The other major exposure history is presented in Table 2.

Laboratory results: Lab results of 47 recipients within the last 2 months were identified and extracted from the database, including blood routine, tacrolimus concentration, liver and kidney function examination (Table 3). The average white blood cell (WBC) count was $7.2\pm2.2\times10^9$/L, 6 (6/47, 12.8%) recipients had an abnormal WBC count including 5 which were elevated. The average neutrophil percentage was 60.4±12.1%, 5 recipients were abnormal. The average lymphocyte percentage was 27.7±9.9%, while 10 (10/47, 21.3%)

recipients had lymphopenia and 31 (31/47, 66.0%) recipients had a lym% lower than 30%. The average tacrolimus concentration was 7.6±2.4ng/mL, which was therapeutic. Examination of liver and renal function was evaluated by ALT, AST, Urea and Creatinine assessments and the average results were grossly normal, while recipients 5 and 6 recipients had liver or kidney insufficiency respectively.

Clinical characteristics of recipients with airway infection: There were 4 upper airway infections reported during this time period (Table 4). 3 of them have been tested for SARS-CoV-2 infection and were negative. The other recipient with upper airway infection recovered after 6 days and was not tested for SARS-CoV-2, because the specific test kit has not yet launched during the early stage of SARS-CoV-2 epidemic. All of them were tested for Flu A and B, and 1 upper airway infection recipient was confirmed with Flu A infection. All of the 4 recipients successfully recovered after proper therapies.

DISCUSSION

This is the largest comprehensive report of HTx recipients during the SARS-CoV-2 epidemic and our findings indicated that this immunocompromised population received similar exposure, including contacting with individuals with travel from Wuhan, taking public transport, going to crowded places, however they exhibited less infection than expected.

The origins of this virus have been traced back to the seafood wholesale market in Wuhan, China.[4] In our epidemiologic investigation, 16 recipients experienced contact with animals or poultry, but there was no reported animal death. No recipients have ever been to the seafood wholesale market in Wuhan or were in contact with any potential supply chains of wild or game meat.

SARS-CoV-2 mainly spreads through the respiratory tract, and survival time of SARS-CoV-2 in air may be somewhat limited. Any protective measures that block the transmission pathway can reduce the risk of infection. According to our investigation of epidemiologic history, it would be reasonable to infer that although HTx recipients have the similar epidemiologic history as normal population, they may have a better protection awareness and use of precautions as a usual practice, during SARS-CoV-2 epidemic.

Studies have shown that people are generally susceptible to coronavirus. Coronaviruses (CoVs), such as SARS-CoV and MERS-CoV, also caused severe lower respiratory tract infection with acute respiratory distress syndrome (ARDS), extrapulmonary manifestations and multiorgan dysfunction syndrome (MODS), among both immunocompetent and immunocompromised hosts with mortality rates of 10% and 35%, respectively.[10, 11] Early patient reports from SARS-CoV-2 find similar trends. Severe manifestations even death with SARS-CoV-2 has been associated in elderly patients with comorbidities, including hypertension, diabetes, heart and/or kidney disease.[3] This finding is similar to increased severity and death in elderly patients following both SARS and MERS-CoV infection.[12, 13] For the MERS-CoV outbreak, smoking, hypertension, diabetes, cardiovascular disease, and/or other chronic illnesses were present in the majority of deaths and correspond to findings in animal models.[14] The accompanying comorbidities in this group of HTx recipients include: hypertension 28 cases (34.2%), hyperlipidemia 15 cases (17.2%), diabetes 20 cases (23.0%), new onset coronary heart disease 1 case (1.1%), chronic obstructive pulmonary disease 1 case (1.1%), cerebrovascular disease 6 cases (6.9%), chronic renal dysfunction 11 cases (12.6%),

hyperuricemia 6 cases (6.9%), hypothyroidism 1 case (1.1%), and the average age is 50.5±11.7. Thus, it would indicate vigilance is necessary for these immunocompromised recipients following SARS-CoV-2 infection.

Our results are unexpected since only 4 recipients got airway infection and 3 of them had a negative SARS-CoV-2 result. This is similar with the information from the Organ Transplant Center in our hospital, where only 2 cases were reported with SARS-CoV-2 infection in renal transplantation.[15] Data from Ju Chunrong suggest that the number of SOT recipients in China suffering from SARS-CoV-2 infection are few, including only 9 confirmed cases altogether.[16] With limited data, it is difficult to determine the populations that may be most susceptible to SARS-CoV-2. More data are needed to determine the susceptibility of the immunocompromised population.

Coronavirus (CoVs) are positive-strand RNA viruses, which primarily target mucosal surfaces of respiratory and intestinal tracts to establish an infection.[17, 18] Epithelial cell surface components are exploited as primary receptors to mediate viral entry and the establishment of a viral infection.[19] One integral protease of the renin-angiotensin system (RAS), angiotensin converting enzyme 2 (ACE2), which is a major physiologic regulator of the cardiovascular system, facilitates cellular entry of human CoVs.[20, 21] Most recently, the ACE2 had been identified as a receptor for SARS-CoV-2.[22, 23] ACE2 is thought to be a key regulator in maintenance of RAS homeostasis.[24, 25] Several studies illustrate the possible mechanism of immunosuppressants in activating RAS.[26-30] Ferrario et al. demonstrated that the treatment of cultured astrocytes with Ang-II caused a marked reduction in neural ACE2 mRNA and protein,

mediated with either losartan or both losartan and lisinopril by the AT1 receptor.[31] It is unclear what, if any, difference in the expression of pulmonary ACE2 exists in the presence of immunosuppression and Investigating the difference of ACE2 between the recipients and normal population would provide further evidence.

Similar to SARS-CoV and MERS-CoV infection, patients with SARS-CoV-2 infections exhibit symptoms of viral pneumonia including fever, cough or dyspnea, and bilateral lung infiltration in severe cases. All these three CoVs induce excessive and aberrant non-effective host immune responses that are associated with severe lung pathology, leading to death.[32] The autopsy results of dead patients indicate diffuse alveolar damage (DAD) with alveolar edema, focal hemorrhage and hyaline membrane formation,[33] which are similar to the pathological manifestations of acute respiratory distress syndrome (ARDS).[34] However, most SARS-CoV-2 were mild or moderate cases, meanwhile cases report showed that the clinical manifestations and progression of SARS-CoV-2 infection in renal transplant recipients were generally consistent with common SARS-CoV-2 infected patients.[15] According to our investigation of epidemiologic history, we could not deny the possibility of contacting and getting infected with SARS-CoV-2 in HTx recipients. It is important to note that laboratory data may be misleading in HTx since several of our patients already exhibited lymphopenia which may be a result of use of immunosuppressants which prevent lymphocyte development and proinflammatory cytokines genes expression, such as interleukin (IL)-2, IL-3, IL-4, IFN-γ, and TNF-α.[36-39] Glucocorticoids inhibit immune responses by negative regulating immunocytes,[40-45] and especially weaken the strength of the T-cell receptor (TCR) signal,

which is important in T cells activation and differentiation[46]. Thus, we imply that if HTx recipients were infected with SARS-CoV-2, they may not exhibit typical manifestations in the early stage due to the presence of immunosuppression. Our data suggest that maintaining the blood trough concentration of FK506 at (7.9±2.9) ng/mL is appropriate. Yet the appropriate degree of immunosuppression needs further verification.

There are several limitations in current study. First, the detailed clinical data for the recipients with airway symptoms were not fully extracted due to the variation of the database in different hospitals. Second, it's reported SARS-CoV-2 may have an extremely long incubation time, so longer observation and following-up are warranted. Furthermore, larger sample size will contribute to more reliability of the data. Furthermore, recall bias, which would be hard to avoid in a survey based investigation, should also be noted as a limitation.

In conclusion, according to our investigation we suggest that HTx recipients who used enhanced protection measures during the SARS-CoV-2 outbreak did not have a substantially higher rate of infection among the population. It is also important to note that immunosuppressed patients may not exhibit typical manifestations and might present confusing laboratory data thus obfuscating diagnosis in some cases. These early data will require confirmation as the pandemic establishes around the world.

Table 1. Demographic description of the heart transplant recipients

	Recipients (N=87)
Age, years	
Mean±SD	51±12
Range	14-73
Sex	
Male	63 (72.4%)
Female	24 (27.6%)
Living together with relatives	80 (92.0%)
Anti-rejection therapy compliance	83 (95.4%)
Comorbidity	
Hypertension	28 (32.2%)
Hyperlipidemia	15 (17.2%)
Diabetes	20 (23.0%)
New onset CHD	1 (1.1%)
COPD	1 (1.1%)
Cerebrovascular disease	6 (6.9%)
Renal dysfunction	11 (12.6%)
Gout	6 (6.9%)
Hypothyroidism	1 (1.1%)

Data are mean±SD and n (%). CHD=coronary heart disease, COPD=chronic obstructive pulmonary disease.

Table 2. Exposure history of the recipients

	Recipients (N=87)
Have been to Wuhan	57 (65.5%)
Contact with 2019-nCoV patients	0 (0.0%)
Contact with asymptomatic individual with epidemic history	16 (18.4%)
Precautionary procedure	11/16 (68.8%)
Take public transport	25 (28.7%)
Precautionary procedure	24/25 (96.0%)
Have been to crowded place	19 (21.8%)
Precautionary procedure	18/19 (94.7%)
Attend group events	5 (5.7%)
Precautionary procedure	3/5 (60.0%)
Animal or poultry touch	16 (18.4%)
Animal death	0/16 (0.0%)
Precautionary procedure in the family	84 (96.6%)
Mask	71/84 (84.5%)
Hand wash	75/84 (89.3%)
Sanitization	52/84 (61.9%)
Precautionary procedure in the community	84 (96.6%)
Daily body temperature and symptoms monitoring	63/84 (75.0%)
Unified living supplies purchasing and distribution	59/84 (70.2%)
Community shutting down and no passing	72/84 (85.7%)
Self-quarantine at home	56 (64.4%)
22-28 days	52/56 (92.9%)
15-21 days	3/56 (5.4%)
8-14 days	1/56 (1.8%)

Data are n (%) and n/N (%).

Table 3. Laboratory results of the recipients

	Recipients (N=47)
Blood Routine	
WBC count ($\times 10^9$/L)	7.2±2.2
Abnormal WBC count	6 (12.8%)
Neu%	60.4±12.1
Abnormal Neu%	5 (10.6%)
Lym%	27.7±9.9
<20%	10 (21.3%)
20-30%	21 (44.7%)
30-40%	10 (21.3%)
40-50%	5 (10.6%)
>50%	1 (2.1%)
FK506(ng/mL)	7.6±2.4
<5.0	4 (8.5%)
5.0-7.9	25 (53.2%)
8.0-11.9	16 (34.0%)
≥ 12.0	2 (4.3%)
Biochemistry	
ALT(U/L)	22.6±17.8
AST(U/L)	25.5±18.7
Abnormal ALT or AST	5 (10.6%)
Urea(mmol/L)	8.6±3.0
Cr(umol/L)	92.9±38.4
Abnormal Urea or Cr	6 (12.8%)

Data are mean±SD and n (%). WBC=white blood cell, Neu%= neutrophilic granulocyte percentage, Lym%= Lymphocyte percentage, ALT= alanine aminotransferase, AST= aspartate aminotransferase

Table 4. Clinical characteristics of the recipients with airway infection

Patient No.	Date of onset	Symptom	Blood routine	Test for airway pathogen	Chest CT report	Diagnosis	Treatment	Outcome
No.17	Dec.31,2019	Nasal obstruction	WBC 11.34×10^9 Neu% 71.6% Lym% 18.7%	SARS-Cov-2(N/A), FluA(-),FluB(-)	Negative	Upper airway infection	Antibiotics	Recovered
No.44	Jan.28,2020	Fever, nasal obstruction	WBC 6.36×10^9 Neu% 76.4% Lym% 13.9%	SARS-Cov-2(-), FluA(+),FluB(-)	Negative	Upper airway infection; Influenza A	Antibiotics, Anti-viral drugs	Recovered
No.58	Feb.2,2020	Dry cough	WBC 5.3×10^9 Neu% 89.5% Lym% 5.7%	SARS-Cov-2(-), FluA(-),FluB(-), HPIV(-),RSV(-), Adv(-), Mpn(-), Cpn(-)	Viral pneumonia	Lower airway infection, viral pneumonia	Antibiotics, Anti-viral drugs	Recovered
No.70	Jan.19,2020	Fever	WBC 4.3×10^9 Neu% 74.7% Lym% 12.3%	SARS-Cov-2(-), FluA(-),FluB(-), HPIV(-),RSV(-), Adv(-), Mpn(-), Cpn(-)	Pulmonary infection	Lower airway infection, pulmonary infection	Antibiotics	Recovered

WBC=white blood cell, Neu%= neutrophilic granulocyte percentage, Lym%= Lymphocyte percentage, HPIV=parainfluenza virus, RSV=respiratory syncytial virus, Adv=adenovirus, Mpn=mycoplasma pneumo, Cpn=chlamydia pneumoniae, CT=computed tomography, (-)=negative, (+)=positive, N/A=not applied

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Ethical approval: This study was approved by the ethical review committee of Renmin Hospital of Wuhan University.

Editor's Note: The article published from China may include patients transplanted at a time when concerns existed with unethical procurement of organ donors, and therefore may represent a violation of the publication policy. However, the editors have chosen to override this aspect, due to the critical importance of the information provided in such a paper for the benefit and help of our patients while recognizing the dignity of those from whom the unethical organs were most probably obtained.

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