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Epidemiologic and clinical characteristics of heart transplant recipients during the 2019 coronavirus outbreak in Wuhan, China: A descriptive survey report

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KEYWORDS:
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BACKGROUND: The epidemiologic and clinical characteristics of heart transplant (HTx) recipients during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic remains unclear. We studied the characteristics of HTx recipients from December 20, 2019, to February 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 the average age was 51 years). A total of 79 recipients resided in Hubei, and 57 recipients had a Wuhan-related history of travel or contact. Most took precautionary measures while in contact with suspicious crowds, and 96.6% of the families and communities undertook prevention and quarantine procedures. Four upper airway infections were reported, and 3 of them tested negative for SARS-CoV-2 (the fourth 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. Of these, 21.3% of recipients had pre-existing lymphopenia, and 87.2% of recipients had a therapeutic concentration of tacrolimus (5−12 ng/ml). Liver and kidney insufficiency was seen in 5 and 6 recipients, respectively.

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

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See Related Editorial, page 405

Since December 2019, a type of novel coronavirus (CoV) infection, later named severe acute respiratory syndrome −CoV 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, broke out in Wuhan, Hubei, China.[1−3] The virus targets the airway epithelium using angiotensin-

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converting enzyme 2 (ACE2) as a receptor and causes a novel CoV-related pneumonia. Some severe cases develop into acute respiratory distress syndrome (ARDS), which can be fatal.[4] The infection spread throughout China and worldwide within 2 months. As of February 25, 2020, a report from the World Health Organization indicated a total of 81,109 lab-confirmed cases from 38 countries and regions. Of those, China had more than 78,000 cases, and deaths had exceeded 2,700.[5]

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

Solid organ transplantation recipients, including heart transplant (HTx) recipients, have a higher infection risk than the normal population because of immunosuppression by anti-rejection therapy.[8,9] However, epidemiologic and clinical characteristics of HTx recipients during the SARS-CoV-2 epidemic are 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 and January 2020 in our hospital were included in this retrospective, single-center study and numbered from 1 to 87 by date of transplantation. We obtained personal information, transplantation-related history, epidemiologic 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. The 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 2 independent investigators. This study was approved by the ethics committee of Renmin Hospital of Wuhan University. Our study complies with the International Society for Heart and Lung Transplantation ethics statement.

Continuous variables were expressed as mean (standard deviation) if they were normally distributed or median (interquartile range) if they were not. Categorical variables were expressed as count and frequency. All statistical analyses were performed using 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 were 63 men and 24 women, the average age was 51 ± 12 years, 80 (92.0%) of them lived together with relatives, and the number of relatives ranged from 1 to 8. A total of 83 (95.4%) recipients followed the pre-defined anti-rejection therapy, and there were no rejection episodes in the past 2 months, whereas 2 patients were admitted to the hospital because of 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%), and hypothyroidism (1 case, 1.1%). All recipients with comorbidities were prescribed with corresponding drugs by specifically trained physicians.

Table 1 Demographic Description of the Heart Transplant Recipients

Demographic	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%)

Abbreviations: CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease.
Data are expressed as mean ± SD and n (%).

Epidemiologic and exposure history

A total of 79 recipients lived in Hubei Province, whereas 57 recipients had a Wuhan contact-related history. The whole group reported no obvious contact with patients with confirmed or suspected SARS-CoV-2–associated disease COVID-19. Protective procedures were initiated with 11 of 16 recipients (68.8%) who were in contact with asymptomatic individuals who traveled to or came back from Wuhan. After January 23, 2020, 84 of 87 recipients (96.6%) undertook precautionary procedures in their community. Of these 87 recipients, 56 (64.4%) self-quarantined at home by more than 1 week. The other major exposure history is presented in Table 2.

Laboratory results

Laboratory results of 47 recipients within the last 2 months were identified and extracted from the database, including

Table 2 Exposure History of the Recipients

Exposure history	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%)

Abbreviation: nCoV, novel coronavirus.
Data are expressed as n (%) and n/N (%).

Table 3 Laboratory Results of the Recipients

Lab result	Recipients (N = 47)
Blood routine	
WBC count ($\times 10^9$ cells/liter)	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/liter	22.6 ± 17.8
AST, U/liter	25.5 ± 18.7
Abnormal ALT or AST	5 (10.6%)
Urea, mmol/liter	8.6 ± 3.0
Cr, μmol/liter	92.9 ± 38.4
Abnormal Urea or Cr	6 (12.8%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; Lym%, lymphocyte percentage; Neu%, neutrophilic granulocyte percentage; WBC, white blood cell.
Data are mean ± SD and n (%).

blood routine, tacrolimus concentration, and liver and kidney function examination (Table 3). The average white blood cell count was 7.2 ± 2.2 × 10^9 cells/liter, and 6 (6 of 47, 12.8%) recipients had an abnormal white blood cell count, including 5 that were elevated. The average neutrophil percentage was 60.4% ± 12.1%, 5 recipients were abnormal. The average lymphocyte percentage was 27.7% ± 9.9%, although 10 (10 of 47, 21.3%) recipients had lymphopenia and 31 (31 of 47, 66.0%) recipients had a lymphocyte percentage lower than 30%. The average tacrolimus concentration was 7.6 ± 2.4 ng/ml, which was therapeutic. Examination of liver and renal function was evaluated by alanine aminotransferase, aspartate aminotransferase, urea, and creatinine assessments, and the average results were grossly normal, although 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). Three of them were tested for SARS-CoV-2 infection and were negative. The other recipient with an upper airway infection recovered after 6 days and was not tested for SARS-CoV-2 because the specific test kit had not yet launched during the early stage of the SARS-CoV-2 epidemic. All of them were tested for influenza A and B, and 1 upper airway infection recipient was confirmed with influenza A infection. All 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 contact with individuals with travel from Wuhan, taking public transport, and 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

Table 4 Clinical Characteristics of the Recipients with Airway Infection

Patient number	Date of onset	Symptom	Blood routine	Test for airway pathogen	Chest CT report	Diagnosis	Treatment	Outcome
17	December 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
44	January 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; FluA	Antibiotics, anti-viral drugs	Recovered
58	February 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
70	January 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

Abbreviations: (+), positive; (−), negative; Adv, adenovirus; Cpn, chlamydia pneumoniae; CT, computed tomography; FluA, influenza A; FluB, influenza B; HPIV, parainfluenza virus; Lym%, lymphocyte percentage; Mpn, mycoplasma pneumoniae; N/A, not applied; Neu%, neutrophilic granulocyte percentage; RSV, respiratory syncytial virus; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell.

have a similar epidemiologic history to the normal population, they may have a better protection awareness and use of precautions as a usual practice during the SARS-CoV-2 epidemic.

Studies have shown that people are generally susceptible to CoV. CoVs such as SARS-CoV and Middle East respiratory syndrome (MERS)-CoV also caused severe lower respiratory tract infection with ARDS, extrapulmonary manifestations, and multiorgan dysfunction syndrome 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 have been associated in elderly patients with comorbidities, including hypertension, diabetes, and 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 most 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%), and hypothyroidism (1 case, 1.1%), and the average age is 50.5 ± 11.7 years. Thus, it would indicate that vigilance is necessary for these immunocompromised recipients following SARS-CoV-2 infection.

Our results are unexpected because only 4 recipients got airway infection and 3 of them had a negative SARS-CoV-2 result. This is similar to 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 et al.[16] suggest that the number of solid organ transplantation recipients in China suffering from SARS-CoV-2 infection are few, including only 9 confirmed cases altogether. 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.

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), ACE2, which is a major physiologic regulator of the cardiovascular system, facilitates cellular entry of human CoVs.[20,21] Recently, 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.[31] demonstrated that the treatment of cultured astrocytes with angiotensin-II caused a marked reduction in neural ACE2 mRNA and protein,

mediated with either losartan or both losartan and lisinopril by the AT1 receptor. It is unclear what, if any, difference in the expression of pulmonary ACE2 exists in the presence of immunosuppression, and investigating the difference in ACE2 between the recipients and the 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 3 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 deceased patients indicate diffuse alveolar damage with alveolar edema, focal hemorrhage, and hyaline membrane formation,[33] which are similar to the pathologic manifestations of ARDS.[34] However, most SARS-CoV-2 infections were mild or moderate cases; meanwhile, case reports 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 recipients because several of our patients already exhibited lymphopenia, which may be a result of the use of immunosuppressants that prevent lymphocyte development and proinflammatory cytokines gene expression, such as IL-2, IL-3, IL-4, interferon-γ, and tumor necrosis factor-α.[35–38] Glucocorticoids inhibit immune responses by negatively regulating immunocytes[39–44] and especially weaken the strength of the T-cell receptor signal, which is important in T-cell activation and differentiation.[45] Thus, we imply that if HTx recipients are infected with SARS-CoV-2, they may not exhibit typical manifestations in the early stage because of the presence of immunosuppression. Our data suggest that maintaining the blood trough concentration of FK506 at 7.9 ± 2.9 ng/ml is appropriate. However, the appropriate degree of immunosuppression needs further verification.

There are several limitations in this study. First, the detailed clinical data for the recipients with airway symptoms were not fully extracted because of the variation of the database in different hospitals. Second, it is reported that SARS-CoV-2 may have an extremely long incubation time, so longer observation and follow up are warranted. Furthermore, a larger sample size will contribute to greater 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.

Disclosure statement

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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 because of 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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