

Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis

Jing-Yu Chen¹, Kun Qiao², Feng Liu¹, Bo Wu¹, Xin Xu³, Guo-Qing Jiao⁴, Rong-Guo Lu¹, Hui-Xing Li¹, Jin Zhao¹, Jian Huang¹, Yi Yang⁵, Xiao-Jie Lu⁶, Jia-Shu Li⁷, Shu-Yun Jiang⁸, Da-Peng Wang⁸, Chun-Xiao Hu⁹, Gui-Long Wang⁹, Dong-Xiao Huang⁹, Guo-Hui Jiao¹, Dong Wei¹, Shu-Gao Ye¹, Jian-An Huang¹⁰, Li Zhou¹, Xiao-Qin Zhang¹, Jian-Xing He³

¹Wuxi Lung Transplant Center, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu 214023, China;

²Department of Thoracic Surgery, Shenzhen Third People's Hospital, Shenzhen, Guangdong 518100, China;

³Department of Thoracic Surgery/Oncology, State Key Laboratory and National Clinical Research Center for Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong 510120, China;

⁴Department of Cardiothoracic Surgery, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu 214023, China;

⁵Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu 210009, China;

⁶Wuxi Fifth Hospital, Wuxi, Jiangsu 214000, China;

⁷Department of Respiratory Medicine and Critical Care Medicine, The First People's Hospital of Lianyungang City, Lianyungang, Jiangsu 222061, China;

⁸Department of Critical Care Medicine, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu 214023, China;

⁹Department of Anesthesiology, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu 214023, China;

¹⁰Department of Respiratory Medicine, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, China.

Abstract

Background: Critical patients with the coronavirus disease 2019 (COVID-19), even those whose nucleic acid test results had turned negative and those receiving maximal medical support, have been noted to progress to irreversible fatal respiratory failure. Lung transplantation (LT) as the sole therapy for end-stage pulmonary fibrosis related to acute respiratory distress syndrome has been considered as the ultimate rescue therapy for these patients.

Methods: From February 10 to March 10, 2020, three male patients were urgently assessed and listed for transplantation. After conducting a full ethical review and after obtaining assent from the family of the patients, we performed three LT procedures for COVID-19 patients with illness durations of more than one month and extremely high sequential organ failure assessment scores.

Results: Two of the three recipients survived post-LT and started participating in a rehabilitation program. Pearls of the LT team collaboration and perioperative logistics were summarized and continually improved. The pathological results of the explanted lungs were concordant with the critical clinical manifestation, and provided insight towards better understanding of the disease. Government health affair systems, virology detection tools, and modern communication technology all play key roles towards the survival of the patients and their rehabilitation.

Conclusions: LT can be performed in end-stage patients with respiratory failure due to COVID-19-related pulmonary fibrosis. If confirmed positive-turned-negative virology status without organ dysfunction that could contraindicate LT, LT provided the final option for these patients to avoid certain death, with proper protection of transplant surgeons and medical staffs. By ensuring instant seamless care for both patients and medical teams, the goal of reducing the mortality rate and salvaging the lives of patients with COVID-19 can be attained.

Keywords: Coronavirus disease 2019; Lung transplantation; Acute respiratory distress syndrome; Pulmonary fibrosis; Sequential Organ Failure Assessment score

Introduction

The outbreak of the coronavirus disease 2019 (COVID-19) caused more than 200,000 reported cases and more

than 8000 people have lost their lives,^[1] and thus, was declared a global pandemic by the World Health Organization.^[2] As reported by Zhong *et al*,^[3] 5.0% of 1099 patients were admitted to the intensive care unit

Access this article online

Quick Response Code:



Website:

www.cmj.org

DOI:

10.1097/CM9.0000000000000839

Jing-Yu Chen and Kun Qiao contributed equally to the work.

Correspondence to: Dr. Jing-Yu Chen, Wuxi Lung Transplant Center, Wuxi People's Hospital affiliated to Nanjing Medical University, Wuxi, Jiangsu 214023, China
E-Mail: chenjiy@wuxiph.com

Copyright © 2020 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2020;133(12)

Received: 15-03-2020 Edited by: Yuan-Yuan Ji

(ICU) and 2.3% received invasive mechanical ventilation (MV). Publications have reported the general characteristics of disease progression with analysis of outcomes, including those of the recovered and mortality cases.^[4] Some patients have prolonged ICU stays due to severe complications, such as acute respiratory distress syndrome (ARDS) and related pulmonary fibrosis, even after results of repeated virological tests are confirmed to be negative. Even with maximal support with MV and extra-corporeal membrane oxygenation (ECMO), such patients showed irreversible deterioration of pulmonary function. We performed lung transplantation (LT) for end-stage patients and hereby present the early results of LT in these recipients. Issues related to the urgent candidate listing of post-COVID-19 critical patients and peri-LT management are further discussed.

Methods

Ethical approval

The lung transplant review and institutional ethics committees of the Shenzhen Third People's Hospital (No. 2020-014) and the Wuxi People's Hospital (No. F2020013) were consulted for urgent LT. Numerous discussions with the patients' family members ensued regarding goals of survival and care while the patients were sedated. All the procedures were approved by the institutional ethics committees. The multidisciplinary team included transplant surgeons, anesthesiologists, physicians, nurses, epidemiologists, physical therapists, respiratory therapists, pathologists, and perfusionists. Volunteer donors were registered in the Chinese organ donation system. Donated lungs were allocated to the urgently listed candidates in accordance with the national organ allocation principles^[5] while considering the priority of urgency related to disease

severity. Organ procurement were performed according to the standard protocol.^[6]

Patient information and data collection

This is a case series-based report of the initial experience on LT for post-COVID-19 patients. Post-COVID-19 patients with pulmonary fibrosis-related ARDS that led to an irreversible pulmonary injury were assessed for LT. From February 10 to March 10, 2020, three male patients were urgently listed, and underwent transplantation. Pre-LT chest imaging confirmed pulmonary consolidation with fibrotic change [Figure 1]. Anti-viral drugs and supportive care were provided as routine protocols to the patients. Tracheostomies have been performed to the three patients. The perioperative demographic and clinical data of the patients were collected and analyzed.

Construction of surgical facilities with high protection level

In view of the high risk of disease transmission and contagion to the surrounding environment by the 2019-novel coronavirus (2019-nCoV), special arrangements were made in 48 h before LT, to guarantee that the appropriate operation room set-up and the necessary protection facilities were available. The hospital where patient 1 was admitted is a regional center for infectious diseases. A special work flow was established for post-COVID-19 LT, and an isolated operation area was created [Figure 2A].

Patient 2 was transported from Lianyungang City to Wuxi City, over a distance of 450 km, escorted by a professional team experienced in handling critical high infectious-risk patients [Figure 2B]. Patient 3 was from Hubei Province and traveled to Wuxi City. He was diagnosed as COVID-19 and admitted directly to the local hospital for

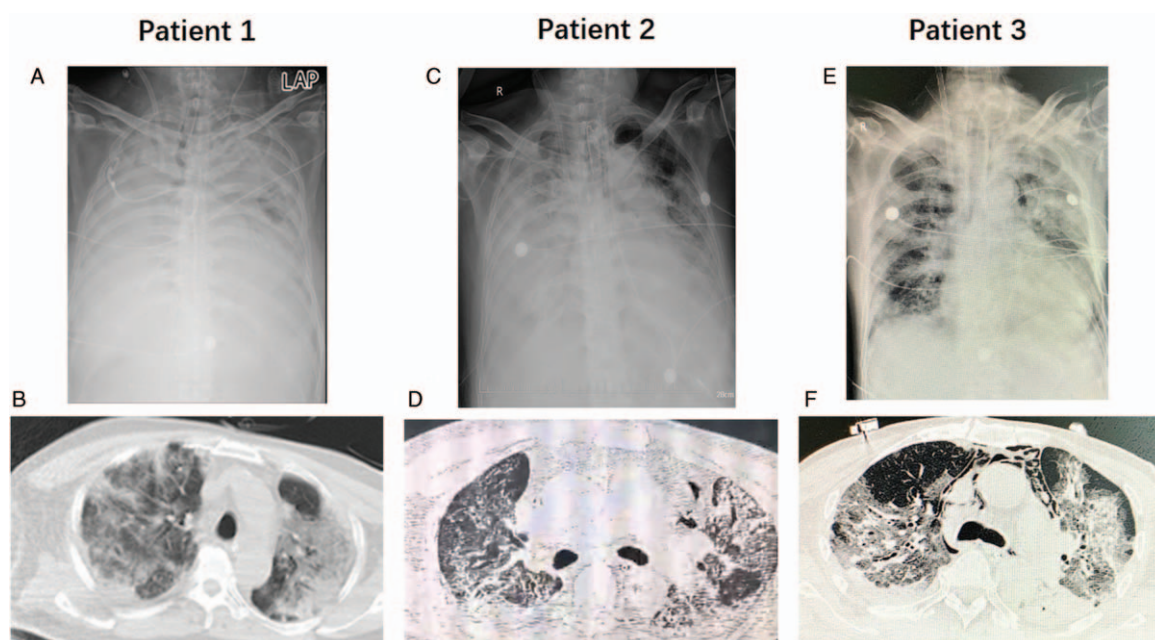


Figure 1: The chest image obtained before LT shows extensive pulmonary consolidation with effusions. Patient 1: (A) radiographic image on pre-LT day 1 and (B) chest CT image on pre-LT day 5. Patient 2: (C) radiographic image on pre-LT day 1 and (D) chest CT image on pre-LT day 5. Patient 3: (E) radiographic image on pre-LT day 2, (F) chest CT image on pre-LT day 1. CT: Computed tomography; LT: Lung transplantation.

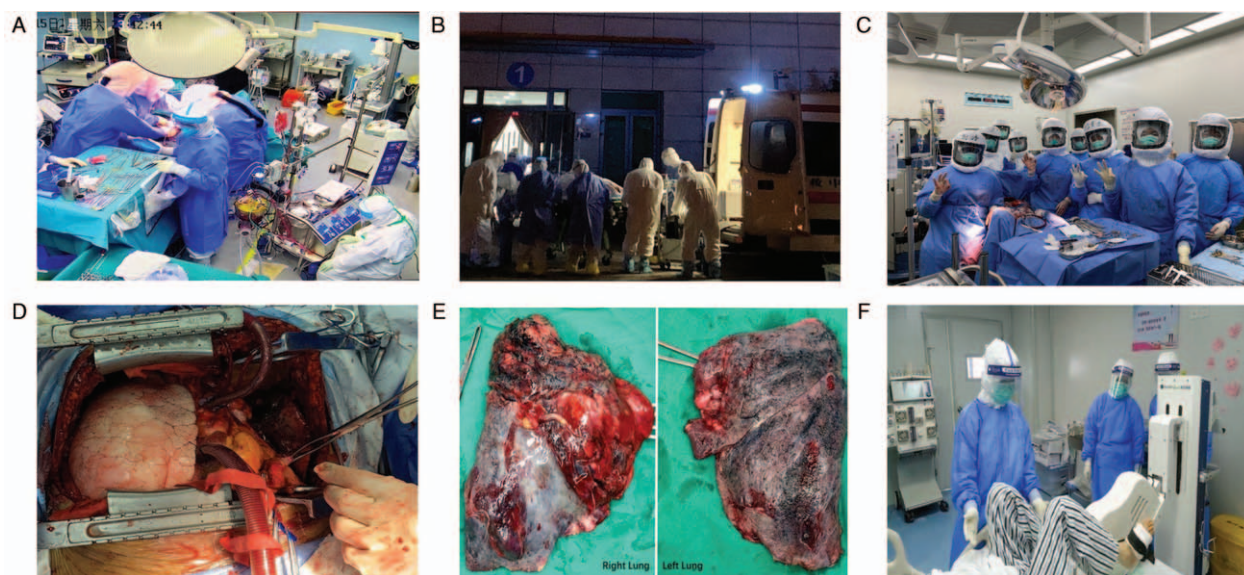


Figure 2: Transplantation logistics and post-LT rehabilitation. (A) The standardized negative-pressure operating room with the medical team fully equipped and remote monitoring for patient 1. (B) Intercity transportation of patient 2 by a protected medical team. (C) Improved operation setup and team collaboration for patient 3. (D) Intra-operative image obtained when the right lung was transplanted and the left lung was about to be explanted in patient 3. (E) Illustration of explanted lungs from patient 3. (F) Early initiation of the rehabilitation program for patient 2, with psychological support from family and friends (blessing cards on the wall). LT: Lung transplantation.

communicable diseases. With the full support of the Provincial Headquarters for Disease Prevention, Control and Treatment, the LT procedure-related operation room setup was constructed in the hospital for communicable diseases in Wuxi City. Wuxi People's Hospital, the largest LT center in China, technically supported the construction of all the facilities, with upgrading of the protection and care systems.

Results

General characteristics before LT

All the recipients were male and aged from 58 to 73 years [Table 1]. Convalescent plasma infusion was performed for all the patients before LT. Coagulopathy was a common manifestation of patients with severe COVID-19 infection. Patient 1 and patient 2 suffered from uncontrolled intra-pulmonary bleeding which could not be controlled by conventional therapy. Thus, urgent assessment for LT was warranted while the patients were using MV and ECMO (veno-venous [VV]-ECMO, cannulated via the right jugular and femoral veins; veno-arterio-venous ECMO for patient 1, cannulated via the right jugular vein, right femoral artery and vein). We cautiously repeated the nucleic acid tests with samples from different sites and confirmed the positive-turned-negative status. However, we intermittently observed some mildly positive results from fecal samples of patient 2. All the patients ultimately showed extremely high pre-LT sequential organ failure assessment scores^[7] and D-dimer values, as shown in Table 1. Comorbidities, as shown in Table 1, were present before COVID-19. Donated grafts were from deceased brain death donors and negative for 2019-nCoV, fully matched with the recipients. Transportation distance of donated organs were 128, 790, and 1470 km,

respectively. The shortest ischemic time could still be guaranteed by steering of green channel for human organ transportation in China.

Pearls of peri-operative management

All the patients were tested negative for a panel of reactive antibodies. Bilateral LT was taken into consideration as the primary choice of treatment. For Patient 1, an additional heart transplantation was also discussed when the medical team anticipated an unstable hemodynamic status with escalation of the inotrope dose. *En bloc* heart and lung procurement was performed pre-LT with allocation approval, giving the transplant team the option to decide, following intra-operative assessment of the recipient, whether heart and LT to be performed.

All the recipients were escorted to the standard negative pressure operating rooms, and the medical team members were fully equipped [Figure 2C]. The patients remained on MV and ECMO, while the exchange of the endotracheal tube to left-sided double-lumen tube was performed by the anesthesiologists. Owing to pulmonary hypertension and related cardiac dysfunction, intra-operative central cannulated veno-arterial (VA)-ECMO was established for all three patients, to support the circulation through the ascending aorta and right atrium at a flow of 3 to 4 L. The right lung was explanted first for all three cases. For patient 2 and 3, the same procedure was performed for the left side [Figure 2D]. Consolidation, extreme pulmonary tissue edema, and congestion with intra-pulmonary hematoma could be observed in all three cases (Figure 2E showed the explanted lungs from patient 3).

For Patient 1, the right lung was transplanted uneventfully. During the left lung transplant procedure, ventricular

Table 1: General characteristics of the three urgently listed LT recipients.

| Characteristics | Patient 1 | Patient 2 | Patient 3 |
|--|------------------------|-----------------------------|-----------------------------|
| Sex | Male | Male | Male |
| Age (years) | 66 | 58 | 73 |
| BMI (kg/m ²) | 27 | 24 | 21 |
| Location | Shenzhen | Wuxi | Wuxi |
| Date of illness | January 3, 2020 | January 23, 2020 | January 26, 2020 |
| Date of confirmation of COVID-19 | January 11, 2020 | January 27, 2020 | February 2, 2020 |
| Comorbidities | Hypertension | HBV infection | DM, CKD, CHD, AF, and COPD |
| Date of MV (days pre-LT) | January 19, 2020 (27) | February 7, 2020 (22) | February 20, 2020 (20) |
| Date of ECMO (days pre-LT) | February 1, 2020 (15) | February 22, 2020 (7) | February 21, 2020 (19) |
| Convalescent plasma | Yes | Yes | Yes |
| Steroids (mg/d) | MP 80 | MP 60 | MP 40 |
| Oxygen index pre-LT (mmHg) | 60 | 104 | 114 |
| Mean PAP (mmHg) | 52 | 48 | 40 |
| ECMO mode pre-LT | VAV (5)+ | VV (3.5)+ | VV (4)+ |
| (flow rate, L/min) | Intra-operative VA (4) | Intra-operative VA (3) | Intra-operative VA (4) |
| Virus-negative samples | NP, BALF, and sputum | NP, BALF, sputum, and serum | NP, BALF, sputum, and serum |
| Lymphocytes pre-LT ($\times 10^9/L$) | 0.41 | 0.70 | 0.58 |
| D-dimer ($\mu g/mL$) | 12.75 | >20 | 13.34 |
| SOFA score pre-LT | 16 | 14 | 18 |
| Date of LT (days of illness onset) | February 15, 2020 (42) | February 29, 2020 (37) | March 10, 2020 (44) |
| Graft location (km) | Guangzhou City (128) | Kaifeng City (790) | Guangzhou City (1470) |
| Incision and LT type | Clamshell, RSLT + HT | Clamshell, Bilateral LT | Clamshell, Bilateral LT |
| Intra-operative cardiac event | VF | No | AF |
| Cold ischemic time (right lung/left lung, min) | 360/550 | 480/575 | 400/480 |
| Total surgery duration (min) | 450* | 300 | 295 |
| Post-LT survival | Death on POD 1 | Survival | Survival |
| PaO ₂ /FiO ₂ (mmHg), POD 1 | – | 350 | 420 |
| ECMO weaning (post-LT, h) | – | 37 | 40 |
| Explanted lung virology | Mildly positive | Mildly positive | – |
| Follow-up reach to POD | – | POD 22 | POD 12 |

* Including a heart transplantation. AF: Atrial fibrillation; BALF: Bronchoalveolar lavage fluid; BMI: Body mass index; CHD: Coronary heart disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; COVID-19: 2019 coronavirus disease; DM: Diabetes mellitus; ECMO: Extra-corporeal membrane oxygenation; HT: Heart transplantation; FiO₂: Fraction of inspiration O₂; LT: Lung transplantation; MP: Methylprednisolone; MV: Mechanical ventilation; NP: Nasopharynx; PAP: Pulmonary artery pressure; POD: Post-operative day; RSLT: Right single lung transplantation; SOFA: Sequential Organ Failure Assessment; VAV: Veno-arterio-venous; VF: Ventricular fibrillation; VV: Veno-venous.

fibrillation developed abruptly and the heart arrested. Cardiac massage was commenced and cardiopulmonary bypass was established with cannulation via the superior, inferior vena cava and ascending aorta, instead of VA-ECMO. Emergent heart transplant was performed. The heart was resuscitated to normal rhythm with strength; however, bleeding from the chest cavity and anastomosis could not be managed with sutures and coagulation in the following 5 h. The transplanted heart arrested again, and the patient was pronounced dead.

In Patient 2, a relatively narrow space in the left chest cavity was observed, and a lobar lung transplant using the left upper lobe was performed. As for patient 3, when the left lung was explanted, the patient developed recurrent atrial fibrillation, causing hemodynamic instability. With intensive intra-operative medical management, the left LT was performed as planned. Both patients 2 and 3 were weaned off their intra-operative VA-ECMO support, and the pre-LT VV-ECMO was maintained with low-dose inotropes. The patients were escorted and monitored in isolated negative pressure ICUs.

Post-LT survival status and explant pathology

Both patients 2 and 3 survived post-LT and regained consciousness on post-operative day (POD) 1. Continuous renal replacement therapy was commenced to achieve negative fluid balance and restoration of renal function. The patients were weaned from VV-ECMO 37 h (patient 2) and 40 h (patient 3) after LT, with grafts fully expanded [Figure 3]. Cyclosporine A was prescribed at a dose (100 mg/d) lower than the conventional initial dose, with gradual tapering according to immune status. Ganciclovir (200 mg/d), antibiotics, and anti-fungal agents were administered per institutional protocol without special treatment for 2019-nCoV. The rehabilitation programs for both patients were initiated early after LT and involved swallowing, limb movements, sitting, and muscle strength training. As the patients had pre-LT tracheostomy, respiratory rehabilitation was initiated with intermittent weaning off MV and respiratory muscle training on POD 3 for patient 2, who gradually progressed to standing balance training on POD 13. Rehabilitation was initiated for patient 3 on

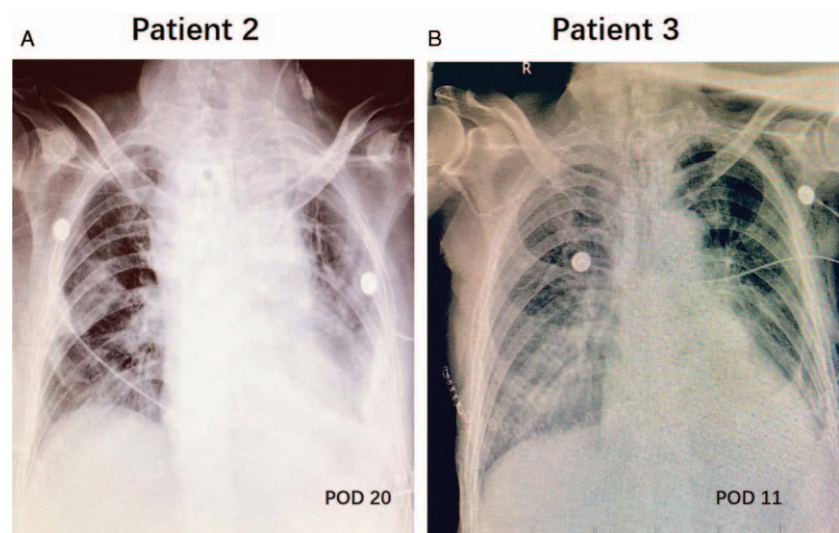


Figure 3: Post-LT images demonstrated fully expanded lung grafts. (A) Radiographic imaging on post-LT day 20 of patient 2. (B) Radiographic image on post-LT day 11 of patient 3. LT: Lung transplantation; POD: Post-operative day.

| Table 2: Representative comparison of explant pathologies. | | | |
|--|--|---|---|
| Items | Gross appearance | Pulmonary parenchyma | Intra-pulmonary vessels |
| National Guidelines (Seventh Edition) | Consolidation with a large amount of mucus plugs | Effusions with hyaline degeneration and fibrosis | Hemorrhagic infarction with micro-thrombosis |
| Patient 1* | Congestive and hemorrhagic necrosis | Extensive pulmonary interstitial fibrosis with hyaline degeneration | Occluded vessel lumen with micro-thrombosis |
| Patient 2† | Congestive and hemorrhagic necrosis | Extensive pulmonary interstitial fibrosis and alveolar hemorrhage | Intravascular organized thrombosis and vasculitis |

* Published in preprints (www.preprints.org) by Luo WR *et al.* Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). March 2, 2020^[9]. † By courtesy of Prof. Feng Chen.

POD 2. Patient 2 could be weaned off MV up to 8 h a day on POD 22 and 3 h for patient 3 on POD 12. Bronchoscopy was performed consecutively for 3 days post-LT and every other day from POD 4 on. There were no abnormal findings but a routine clearing of airways. Chest tubes were removed on POD 5 for both patients. Follow-up days were showed in Table 1. Patients 2 and 3 are alive and still admitted in isolated negative-pressure wards. Regularly nucleic acid tests results from samples of bronchoalveolar lavage fluid, nasopharynx, serum, and fecal were all negative. We keep on monitoring the virus tests. If still negative up to 30 days post-LT, we are planning to move the patients to general ward with routine care.

When examining the explanted lungs from patients 1 and 2 and comparing the pathological characteristics recorded in the national guidelines for COVID-19,^[8] we observed a more severe pulmonary injury [Table 2]. Generally, extensive hemorrhage and fibrosis occurs in patients with end-stage ARDS post-COVID-19.^[9] Effusions and sputum bolts in small airways, extensive thrombosis, and secondary hemorrhage had further impaired the gas exchange, accelerating the irreversible deterioration of the lung function.

Discussion

Best time to perform transplantation in critical patients

This is the first case series report on LT for COVID-19 patients who could not be weaned off ECMO support. Issues related to viral infection course, clinical course of recipients in the long term and staff protection are worthy of further exploration. In the acute care setting, the patients described herein were confirmed to have consecutive negative nucleic acid test results but presented with severe ARDS without lung function recovery. The physicians who treated the patients had difficulty waiting and merely observing the inevitable fatal outcome. LT in severe acute respiratory syndrome (SARS) patients with ARDS has not been reported. However, LT has been performed for patients receiving ECMO for >45 days after H1N1 infection.^[10] ECMO is believed to contribute to lung function recovery in severely infected patients and it serves as a bridge treatment before LT. LT has been shown to be beneficial for patients with pneumonia-induced ARDS and post-ARDS pulmonary fibrosis receiving long-term MV.^[11] The fact that young individuals receiving ECMO for a short time could be considered as candidates for LT after deliberate pre-transplant consultation is generally

accepted.^[12] However, our transplanted patients had higher SOFA scores than those reported in critical COVID-19 populations, indicating a high risk of mortality. LT provided the final option for these patients to avoid certain death.

Key points on determination of LT candidacy

The following three critical points should be thoroughly evaluated and confirmed before decision-making regarding LT candidacy: (1) confirmed irreversibility of refractory respiratory failure despite maximal medical support; (2) confirmed positive-turned-negative virology status by performing consecutive nucleic acid tests with samples derived from multiple sites; and (3) confirmed absence of other organ system dysfunction that could contraindicate LT. LT was regarded as an urgently needed salvage therapy after full evaluation of the pathological condition of the patients. We further discussed the plan for bilateral LT or heart and LT. The consideration of heart transplantation and LT for patient 1 involved the concern that the prolonged procedure time would add to the risks of bleeding and death. Further, 2019-nCoV may attack the cardiac tissue, and indeed, we observed that all the patients had an elevated pulmonary artery pressure related to cardiac dysfunction. Thus, assessment of cardiac function using ultrasonography and monitoring B-type natriuretic peptide levels are crucial steps that can provide information regarding procedural decision making.

Best practices for the protection of the medical team involved

For the protection of the medical team to avoid infection, we provide a detailed and specialized plan based on grade 3 (highest level of protection) protection requirement [Table 3]. Suggestions for protection are as follows: (1) head covers with positive pressure are necessary for surgeons, nurses, anesthesiologists, and cardiopulmonary physicians; (2) head covers will help surgeons keep their field of view clear without fogging of eye protectors; however, these will negatively impact sound conduction, including communication between physicians and alerts from monitors; (3) considering the physical demands and

challenges for surgeons in full protective clothing, an intra-procedure rotation plan is necessary to guarantee optimal performance during surgery.

During the transplantation procedure for patient 1, we used a remote video communication tool to connect the surgical team in the isolated operating room and experts outside the contaminated regions. However, there were still blind-spots and delay for instantaneous communication. As we transplanted patients 2 and 3, coordinators who were responsible for communicating with the staff inside the operating room and supplying medical materials, played crucial roles. Instant voice messages and video images could be transmitted outside the isolated operating room, thereby ensuring the full-scale monitoring and service for surgery. Furthermore, all the operation-related medical staffs rehearsed the procedure before surgery. Considering the difficulty of direct communication while wearing head covers during surgery, gestures, and actions that indicated the need for assistance, the passing of sutures or instruments between surgeons and nurses allowed for non-verbal communication.

By gaining more experience regarding the comprehensive logistics of LT for patient 2 in Wuxi, the Wuxi group managed the key steps and thoroughfares that led to the successful LT. LT for these patients was seemingly unimaginable due to high risk of contagion and challenges on team collaboration and psychological strength. However, all the obstacles were overcome within a shorter operation time of less than 5 hours than that in conventional LT. So far, no infection event has been noted among the members of the medical team.

Factors important for post-LT survival

During the SARS infection outbreak, medical resources in China, such as experienced ECMO teams and fully protective negative pressure operating rooms, were scarce. Further, transportation of donated lungs over long distances for urgently listed patients post-ARDS was impossible. The volunteer organ donation volume in China has reached up to 6000 cases per year recently. However, the usage percentage of donated lungs is around 5%,

Table 3: Considerations and comparisons of surgical preparations.

| Items | LT for post-COVID-19 patient | Non-urgent LT |
|--------------------------|---|------------------------------------|
| Procedure | Bilateral lung transplantation | Depends on the patient's condition |
| Operating room setup | Grade 3 protection | Sterile environment |
| Patient's condition | Potential contagiousness | Non-contagious |
| Surgeon's alertness | Impaired alertness because of the head cover | Swift response to alert sound |
| Rehearsal before surgery | Symbolization of actions during surgery to supplement voice communication | Not applicable |
| Operation field | Controlled but acceptable | No impact |
| Coordinator | Specialized for inside-and outside-operating room liaison by audio/video | Not applicable |
| Communication | Difficulty of collaboration with staffs | No impact |
| Physical challenge | Prone to exhaustion | Manageable |
| Cost | High | Manageable |

COVID-19: 2019 coronavirus disease; LT: Lung transplantation.

significantly lower than that of roughly 25% in western countries. All the three recipients were transplanted with the officially allocated organs through national allocation system. Currently, the Chinese organ donation system and green channel for human organ transportation play pivotal roles in achieving patient survival after LT.^[13]

Rehabilitation procedures have been well established for patients who have undergone a conventional LT. Early mobilization for our post-COVID-19 patients provided enormous strength to pursue a good quality of life [Figure 2F]. The patient started advanced rehabilitation with fully functional grafts. As can be inferred from our current experience, patients with irreversible pulmonary fibrosis related to ARDS post-COVID-19 can be scrutinized for the possibility of LT. However, the duration of isolated ward admission was extremely long in our patients. Moreover, the medical team involved was instructed not to leave the isolated area and was separated from their families. Taken together, psychological assistance, including modern social media platform and communication tools, would best enhance the confidence of both the patients and medical teams while striving for survival.

With negative nucleic acid test results, positive IgG were detected in patients 2 and 3. No virological relapse was noted. Although a mild positive nucleic result could be observed from fecal sample of patient 2, this patient had confirmed negative results in fecal samples post-LT. We speculated that the positive result could be derived from nucleic acid segments or components from residue virus without further infectivity, thus providing an explanation of the mild positive results from explants. This still warrants further close follow-ups and research.

In the future, patients' immune status regulated by therapeutic regimens and interaction with potential infection events should be evaluated. A previous report indicated that the cytokine profiles of ICU-admitted COVID-19 patients were greatly altered,^[14] which might contribute to immune imbalances and multi-organ dysfunction. LT and immunosuppressive regimens could ameliorate these severe pathological conditions. More data and evidence are still urgently needed to evaluate the long-term benefits of this salvage therapy.

Perspective

With careful protection and complete preparation of the patients and surgeons, the success of LT can be ensured, thereby reducing the high mortality rate of end-stage COVID-19 patients. The success of LT in our post-COVID-19 patients was credited not only to the medical team but also to the dedication of the public health and pathology teams with P3 laboratory-based research capability. A more precise pathophysiological knowledge prompts clinicians to establish a targeted treatment plan. Overall teamwork supported by government systems played fundamental roles in the LT of our patients. The swift response of regulatory departments for approval of nucleic acid test tools would further ensure credible disease monitoring and the protection of health-care providers.

Funding

This study was supported by grants from the Chen Jingyu team of "Sanming Project of Medicine" in Shenzhen (No. SZSM201812058), and the Foundation for Special Projects of COVID-19 Prevention and Control in Wuxi City.

Conflicts of interest

None.

References

1. WHO Director-General's Opening Remarks at the Media Briefing on COVID-19-18 March 2020. Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19>. [Accessed March 18, 2020]
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed* 2020;91:157–160. doi: 10.23750/abm.v91i1.9397.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al.* China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020. doi: 10.1056/NEJMoa2002032 [Epub ahead of print].
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020. doi: 10.1001/jama.2020.1585 [Epub ahead of print].
5. Huang J. The "Chinese Mode" of organ donation and transplantation. *Hepatobiliary Surg Nutr* 2017;6:212–214. doi: 10.21037/hbsn.2017.07.08.
6. Chen JY, Mao WJ, Ma QL, Liu D, Zhao J, Ding H. Chinese lung donation standard and procurement guidelines (In Chinese). *Organ Transplantation* 2018;9:325–333. doi: 10.3969/j.issn.1674-7445.2018.05.001.
7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–1062. doi: 10.1016/S0140-6736(20)30566-3.
8. National Health Commission & National Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7). *Chin Med J* 2020;133. doi: 10.1097/CM9.0000000000000819 [Epub ahead of print].
9. Luo WR, Yu H, Gou JZ, Li XX, Sun Y, Li JX, *et al.* Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints* 2020;2020020407.
10. Wang Q, Pan S, Zhang S, Shen G, Huang M, Wu M. Lung transplantation in pulmonary fibrosis secondary to influenza A pneumonia. *Ann Thorac Surg* 2019;108:e233–e235. doi: 10.1016/j.athoracsur.2019.02.035.
11. Chang Y, Lee SO, Shim TS, Choi SH, Kim HR, Kim YH, *et al.* Lung transplantation as a therapeutic option in acute respiratory distress syndrome. *Transplantation* 2018;2018;102:829–837. doi: 10.1097/TP.0000000000002004.
12. Salam S, Kotloff R, Garcha P, Krishnan S, Joshi D, Grady P, *et al.* Lung transplantation after 125 days on ECMO for severe refractory hypoxemia with no prior lung disease. *ASAIO J* 2017;63:e66–e68. doi: 10.1097/MAT.0000000000000450.
13. Wu B, Hu C, Chen W, He J, Jiang G, Zhang J, *et al.* China lung transplantation developing: past, present and future. *Ann Transl Med* 2020;8:41. doi: 10.21037/atm.2019.10.26.
14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5.

How to cite this article: Chen JY, Qiao K, Liu F, Wu B, Xu X, Jiao GQ, Lu RG, Li HX, Zhao J, Huang J, Yang Y, Lu XJ, Li JS, Jiang SY, Wang DP, Hu CX, Wang GL, Huang DX, Jiao GH, Wei D, Ye SG, Huang JA, Zhou L, Zhang XQ, He JX. Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis. *Chin Med J* 2020;133:1390–1396. doi: 10.1097/CM9.0000000000000839