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# Lung Transplant as a Treatment for Patients with End-Stage Respiratory Failure Due to COVID-19

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## ABSTRACT

**Background.** COVID-19 may lead to development of irreversible acute respiratory distress syndrome. Some patients sustain severe respiratory failure after infection subsides. They may require lung transplant as a last resort treatment. The aim of the study is to assess the effect and feasibility of lung transplant as a treatment for patients with severe irreversible respiratory failure due to COVID-19.

**Methods.** This retrospective study pertains to analysis of 119 patients in critical condition who were referred to Lung Transplant Ward (Zabrze, Poland). between July 2020 and June 2021 after developing respiratory failure requiring extracorporeal membrane oxygenation, invasive ventilation, or both, as well as a few patients on high-flow oxygen therapy. Inclusion criteria for referral were confirmed lack of viral disease and exhaustion of other therapeutic options.

**Results.** Of the referred patients, 21.84% were disqualified from such treatment owing to existing contraindications. Among the suitable patients, 75.8% died without transplant. Among all patients who were qualified for lung transplant, only 9 patients became double lung transplant recipients. Intraoperative mortality for this procedure was 33%. Four patients were discharged after the procedure and are currently self-reliant with full respiratory capacity.

**Conclusions.** Patients with severe irreversible respiratory failure after COVID-19 present significantly high mortality without lung transplant. This procedure may present satisfactory results but must be performed in a timely fashion owing to critical condition and scarcity of lung donors, only aggravated around the time of peak infection waves.

SARS-COV-2 has caused a pandemic, which influenced lung transplants in various ways. Since the first wave, it changed donation procedures, decreased number of available organs, as well as caused many people to develop severe acute respiratory distress syndrome (ARDS). COVID-19 left many patients with severe irreversible respiratory failure each month of the pandemic, and many of them became dependent on invasive ventilation and/or extracorporeal membrane oxygenation (ECMO) support [1]. Available data show extensive evidence of injury and fibrosis that resembled end-stage pulmonary fibrosis [2]. When all other therapeutic options have been exhausted, some patients might be considered to become lung transplant recipients. Certain criteria have been established in order to assess who would benefit for lung transplant [3]. First and foremost, decision to qualify for such procedure must only be made for patients who do not present any contraindications, not only for transplant but also for lifelong immunosuppressive treatment. Second of all, as the number of worldwide lung transplants is generally limited by scarcity of donors, an ethical framework was established in the form of a consensus statement from the International Society for Heart and Lung Transplantation [4]. The aforementioned framework is based on values such as justice, utility, and efficiency. It states that patients who are the most severely ill must be given highest priority provided they present a high chance of reaching longtime benefits from

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lung transplant. Such approach enables transplant centers to offer transplant as a therapeutic treatment to certain patients who are dependent on invasive ventilation and/or ECMO after COVID-19. It is important to remember that patients with such support have a very limited time to wait for a suitable organ as those therapeutic options provide necessary gas exchange but also are associated with severe, often fatal complications. As COVID-19 was a new disease, it was difficult to assess the potential benefit of lung transplant among those so severely ill. The first known cases of lung transplant as a treatment were published by a Chinese team [5]. In a short time, more and more cases of successful lung transplants for such patients were published [2,6,7]. Due to the severity of the first COVID-19 wave in Poland, many intensive care units and pulmonology departments were contacting our Lung Transplant Team regarding such treatment. Our first patient transplanted due to COVID-19 was a man supported by ECMO for couple of weeks. He underwent double lung transplant on the last day of July 2020 and has successfully reached 1-year posttransplant survival with full respiratory capacity, as we reported [8].

The aim of the study is to assess the effect and feasibility of lung transplant as a treatment for patients with severe irreversible respiratory failure due to COVID-19, as well as to analyze patients who were referred as potential lung transplant candidates.

## MATERIALS AND METHODS

This retrospective study pertained data gathered from 119 potential lung transplant candidates due to irreversible respiratory failure after developing COVID-19 between July 2020 and July 2021. All patients were referred to a single center. Inclusion criteria to begin the qualification process were as follows: confirmed absence of SARS-COV-2 by reverse transcription polymerase chain reaction (RT-PCR) assessment twice with at least 1 day apart; no clinical and radiological signs of improvement over at least 3 weeks after obtaining negative RT-PCR results; lack of severe failure of organs other than lungs. Detailed characteristics of all referred patients are presented in Table 1. Data (age, sex, comorbidities, body mass index, extent of respiratory support) were gathered from standard potential lung transplant recipient questionnaire. Additional assessment of pulmonary function tests was performed for patients who actually underwent lung transplant. Lung function was assessed by means of spirometry (forced expiratory volume in 1 second as percentage of predicted value; forced vital capacity as percentage of predicted value; Tiffeneau-Pinelli index) as well as 6-minute walk test results, particularly distance, oxygen saturation before the test, and after finishing the test.

Patients underwent the procedure in an accredited facility.

**Table 1. General Characteristics of 119 Referred Patients**

| Variable | Value |
|---|---|
| Sex | Male: 74.14%; female: 25.86% |
| Age (y), mean ± SD | 52.02 ± 10.17 |
| BMI (kg/m$^2$), mean ± SD | 29.44 ± 4.17 |
| Respiratory support at referral | ECMO VV 55.36% |
| | MV 32.14% |
| | O2 12.5% |
| Most common comorbidities at referral with their frequency | Obesity 36.5%, systemic arterial hypertension 33.9%, diabetes mellitus type 2 11.3%, confirmed liver steatosis 11.3%, preexisting lung disease 6.8% |

BMI, body mass index; ECMO VV, veno-venous extracorporeal membrane oxygenation; MV, mechanical ventilation; O2, passive oxygen therapy; SD, standard deviation.

## RESULTS

The majority of patients (55.36 %) presented with end-stage respiratory failure with ECMO and invasive mechanical ventilation. All of the potential lung transplant recipients were required to undergo the qualification process, as all of the generally recognized contraindications must have been assessed and excluded. At the time of referral, 21.85% of patients presented with contraindication, with severe kidney failure, impaired neurologic state, and cardiovascular complications being the most common ones. Ninety-three patients were initially cleared to continue the qualification process. However, only 62 patients survived to be properly qualified for lung transplant. Of those who were on a national lung transplant waitlist due to irreversible respiratory failure after COVID-19, 75.8% died without lung transplant. Duration of ECMO support varied among patients. In some cases, it was observed that after a couple of weeks acute respiratory distress syndrome subsided with satisfactory recovery of the lungs. Despite initial severe condition, 6 patients improved to the extent of not needing to be transplant candidates at that time. Nevertheless, their condition and lung function were regularly checked. Nine patients became double lung transplant recipients. Intraoperative mortality was 33%. Two patients (a woman and a man) died in the postoperative period. The female patient developed a severe case of postoperative mediastinitis, which proved to be fatal despite treatment. The other patient's death was contributed to by severe digestive tract bleeding and meningitis. Four patients were discharged from the hospital in general good condition. All four were treated with preoperative ECMO due to end-stage respiratory failure for 4-6 weeks prior to lung transplant. They were treated with immunosuppressive maintenance therapy consisting of tacrolimus, mycophenolate mofetil, and prednisolone. The first patient had his first post-transplant year complicated with few infections, 2 of them requiring intravenous antibiotics. He presented with full respiratory capacity. Damage of the peroneal nerve still persists. However, certain improvement was noted due to extensive physical rehabilitation. The second patient developed airway stenosis, which required endoscopic bronchoplasty more than once during the first year. This patient was also hospitalized 3 times during the first posttransplant year due to infection, with respiratory syncytial virus being the most recent one. He also has reached 1-year survival with satisfactory respiratory capacity. The third patient presented the uneventful clinical course without need for hospitalization except 1-day protocol follow-up visits so far. He reached 9-month survival in December. The fourth patient was a woman who was infected

with SARS-CoV-2 while 29 weeks pregnant. She required an emergency cesarean delivery at 30 weeks and was placed on ECMO support shortly after. She received lung transplant despite almost 50% of panel of reactive antibodies, which necessitated crossmatch assessment. She underwent double lung transplant as its result was unanimously negative. Her early post-transplant clinical course required us to perform tracheostomy due to muscle weakness. Two months after transplant she was discharged as self-reliant with full respiratory capacity without tracheostomy. Nevertheless, a couple of weeks after discharge she began experiencing a severe case of bronchial stenosis, especially within the right bronchial tree, which required frequent endoscopic bronchoplasties. Her clinical course so far during an 8-month follow-up was also complicated with a cytomegalovirus infection, *Pneumocystis jirovecii* pneumonia (twice), and fungal infection (*Aspergillus* spp). Presently, she is self-reliant but requires passive oxygen supply at greater exertion. Her daughter is alive and well and, at 8 months old, does not present any developmental deficits. However, she is under care and supervision from pediatric cardiology due to mild atrial septal defect. Detailed respiratory function of all patients is presented in Table 2.

## DISCUSSION

It became clear that patients in the aforementioned condition were not expected to survive without lung transplant. However, due to lack of data, it was difficult to assess whether they would benefit from this kind of treatment. As the pandemic lasted and more data were gathered, more publications were pointing out the feasibility of lung transplant as a treatment. It was also reported that ARDS due to COVID-19 (CARDS) may subside, leaving the patient with satisfactory respiratory function in a couple of weeks [3]. Careful consideration is advised while qualifying patients for lung transplant after COVID-19. An article published by Cypel and Keshavjee points out lung transplant teams should be certain that the patient's lungs have no significant potential for recovery, as regaining respiratory capacity without transplant seems more beneficial [3]. Additionally, the patient must undergo proper qualification process and cannot present with any contraindications that would prohibit pre−COVID-19 lung transplant. Such opinion is supported by King et al [9]. They report that the major obstacles in patients with severe CARDS treated with ECMO or mechanical invasive ventilation are the inability to conduct proper psychosocial evaluation and pretransplant education, marked deconditioning from critical illness, and infectious concerns pertaining to viral reinfection as well as bacterial pathogens from an intensive care unit. Limited knowledge about the natural history of recovery after COVID-19 infection was also assessed as problematic. Volume of the chest, particularly in both pleural cavities, may significantly decrease in the course of COVID-19. Proper sizing of 1:1 or less is advised by Urlik et al [8]. The authors of this paper took the liberty of more liberal size-matching of the lungs due to critical condition of the patient and increasing risk of ECMO-related fatal complications [8]. The first reported cases of lung transplant as a treatment of post −COVID-19 respiratory failure pertained to 66- and 70-year-old Chinese patients [5]. Despite a thorough report, certain issues (need for post-transplant ECMO, age of the patients, and lack of description for more than a couple of days follow-up) were concerning. Those issues as well as lack of transparency of the Chinese solid organ transplant programs were also voiced by Baquero et al [10]. Over time, more reports emphasizing different aspects of lung transplants due to COVID-19 were occurring [6,11,12]. An Austrian team performed lung transplant for a 44-year-old woman with positive RT-PCR results after assessing viral activity by Vero cultures as negative after 7 days in 3 passages, as described by Lang et al [7]. This case report shows limitations of RT-PCR testing. However, viral activity and presence must be excluded with high certainty. Hawkins et al carried out the systematic review regarding the topic of lung transplant as a treatment for post−COVID-19 respiratory failure [13]. Based on 21 cases of lung transplants worldwide, they evaluated the early survival rate at 95% even though 85% of described recipients required preoperative ECMO. During almost 2 years of the pandemic, technical feasibility of lung transplant after proper thorough qualification process seems to be established. However, other important issues should also be taken under consideration. Lepper et al [14] wrote an interesting comment to the case series published by Bharat et al [2]. A German team was concerned that as lung transplant faces the scarcity of donors, each lung must be used for patients who have general good prognosis of surviving a couple of years with transplant despite presenting with end-stage respiratory failure before procedure. To quote Lepper et al, "The success of a transplant procedure cannot solely be judged by the fact that a patient can be discharged from the ICU" [14 (p e88)]. Another concern is that, by accepting high-urgency candidates with ARDS during the pandemic, lung transplant teams will disadvantage patients on the waiting list, increase waiting-list mortality, decrease post-transplant survival, and distort the discriminatory capacity of any organ allocation systems [15]. In

**Table 2. Lung Function of Patients, Who Were Discharged After Lung Transplantation due to COVID-19**

| Respiratory support<br>Tracheostomy | Patient 1<br>ECMO VV<br>No | Patient 2<br>ECMO VV<br>No | Patient 3<br>ECMO VV<br>No | Patient 4<br>ECMO VV<br>Yes |
|---|---|---|---|---|
| Discharge | | | | |
| FEV1 | 57% | 54% | 59% | 48% |
| FVC | 51% | 49% | 59% | 63% |
| 6MWT | | | | |
| Distance (m) | 463.4 | 280.8 | 320 | 405. 6 |
| Pre-sat | 100 | 99 | 99 | 94 |
| Post-sat | 99 | 97 | 99 | 88 |
| 6-month follow-up | | | | |
| FEV1 | 66% | 52% | 64% | 42% |
| FVC | 60% | 81% | 72% | 57% |
| 6MWT | | | | |
| Distance (m) | 588.2 | 510.5 | 612 | 534.5 |
| Pre-sat | 99 | 96 | 99 | 95 |

6MWT, 6-minute walk test; ECMO VV, veno-venous extracorporeal membrane oxygenation; FEV1, forced expiratory volume in first second; FVC, forced vital capacity; Sat, saturation.

conclusion, Lepper et al agree that lung transplant can be an option for certain patients after careful consideration. A French team also voices their concerns, as Messika et al reminds that the healing potential of lung parenchyma should not be underestimated, even after 50 days of ECMO support with some patients regaining respiratory capacity after 90 days on ECMO [16]. On the other hand, Kurihara et al made an assessment of patients who were treated with ECMO due to end-stage lung failure in course of COVID-19 [17]. Even though CARDS was not associated with a higher post-ECMO mortality than patients with ARDS unassociated with COVID-19, patients with CARDS presented with significantly higher rates of bleeding and thrombotic complications. What is more, 100% of patients who were on invasive ventilation for longer than 7 days prior to ECMO died without lung transplant.

Such examples of concern are important as during 2020, COVID-19 and its complications were unknown and all the patients were treated with the best care and knowledge accessible at the time. Now, in 2022, more than a year has passed since the introduction of the efficient vaccines against this virus [18]. The adult population in Poland was granted nationwide, unlimited access to free vaccination against SARS-CoV-2 on May 10, 2020 [19]. However, vaccine hesitancy is reported to be 48.5% among men and 45.6% among women (particularly those younger), with the main reason for the entire study group being the fear of vaccine side effects [19]. A safe and effective vaccine offers direct (high-risk groups are vaccinated to prevent disease) and indirect (those in contact with high-risk individuals are vaccinated to reduce transmission) protection [20]. It seems to be the only way of ending the COVID-19 pandemic, which hopefully will restore full capacity of performing lung transplants in regard to availability of the donors. However, many potential lung transplant candidates will still remain after the pandemic is over. All of the aforementioned articles regarding lung transplant were published before effortless, free-of-charge access to efficient vaccines. The newest consensus statement published by the International Society for Heart and Lung Transplantation pertains to the topic of qualification for this procedure [21]. Survivors of COVID-19 should be evaluated for transplant only if they have demonstrated lack of clinical improvement, persistent parenchymal infiltrates, as well as severely reduced lung compliance after prolonged support. It was also assessed that it is too early to make more conclusive recommendations now [21]. According to the society's initial statement, lung transplant programs should have the explicit goal of maximizing long-term survival in order to provide net survival gains for society as a whole. It is also explained as an unsuccessful lung transplant also affects a potential alternative recipient who did not have the opportunity to be transplanted due to the prevailing organ shortage, especially aggravated during each COVID-19 wave. In the autumn and winter 2021 COVID-19 wave in Poland, a significant majority of patients referred for lung transplant were not vaccinated against SARS-CoV-2, by choice. This creates an ethical dilemma as to whether patients who are not increasing net survival gains for society (by disagreeing to be immunized by vaccine), therefore not ensuring direct and indirect protection, as well as using the scarce resources in case of developing CARDS, should be considered for lung transplant.

## CONCLUSIONS

Patients with severe irreversible respiratory failure after COVID-19 present significantly high mortality without lung transplant. This procedure may present satisfactory results but must be performed in a timely fashion due to critical condition and scarcity of lung donors, only aggravated around the time of peak infection waves. Proper qualification process is essential.

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## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.transproceed.2022.03.017.

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