Peer Review File

Article information: https://dx.doi.org/10.21037/shc-22-2

Reviewer A

Comment 1: I suggest reviewing how the follow-up of these patients would be carried out
Reply 1: thank you for your suggestion. We added a paragraph at the end of the case description.
Changes in the text: we added a paragraph at the end of the case description section: "Follow-up was carried out according to the local post-transplant guidelines, which includes regular controls of blood gas exchange and spirometry. Outpatient gastroenterological consultations were also booked to monitor for esophageal dysfunction generally linked to the initial diagnosis of SSc." (see Page 8, line 167-180)

Comment 2: Review Image 1
Reply 2: thank you for your suggestion. We changed previous image 1 with a clearer one.

Comment 3: And finally, expose which groups made the decision to place the patient on the transplant list
Reply 3: thank you again for your valuable comment. We added the followup statement in the case description
Changes in the text: we added these words in the case description section: "the multidisciplinary lung transplant team of our hospital, which includes respiratory physician, thoracic and cardiac surgeons, anaesthesiologist and intensivist care specialists, decided to list the patient for an urgent bilateral lung transplant on October 3, 2020."
(see Page 8, line 138-141)

Reviewer B

The authors present a case of the patient with systemic scleroderma and end-stage lung failure for which reason he underwent a successful LTx after being bridged with VV ECMO.
However, I have several comments that limit the scientific value of the manuscript.
Comment 1: Why the authors believe this case report has novelty? While there are many reports of LTx in the setting of systemic scleroderma, authors did not cite them, Panchabi et al. have summarized 11 articles with this topic. Please add more references related to LTx in SS and bridge with ECMO:
a) Panchabhai TS, et al Lung Transplant in Patients with Connective Tissue Diseases. Clin Chest Med. 2019 Sep;40(3):637-654. doi:10.1016/j.ccm.2019.05.009.
b) Richardson CB, et al. Lung Transplantation for Scleroderma-related Lung Disease. Curr Respir Care Rep. 2014 Sep;3(3):79-87. doi:10.1007/s13665-014-0080-6.

c) Gleason JB, et al. Pulmonary Artery Dimensions as a Prognosticator of Transplant-Free Survival in Scleroderma Interstitial Lung Disease. Lung. 2017 Aug;195(4):403-409. doi:10.1007/s00408-017-0005-6.
d) Sef D, et al. Midterm outcomes of venovenous extracorporeal membrane oxygenation as a bridge to lung transplantation: Comparison with non bridged recipients. J Card Surg. 2022 Apr;37(4):747-759. doi: 10.1111/jocs.16253.
e) Biscotti M, et al. Awake Extracorporeal Membrane Oxygenation as Bridge to Lung Transplantation: A 9-Year Experience. Ann Thorac Surg. 2017 Aug;104(2):412-419. doi:10.1016/j.athoracsur.2016.11.056.
Reply 1: thank you for this valuable comment. As you know, lung transplant in the setting of scleroderma is unusual and most of the articles include limited numbers of patients. Moreover, almost all of them consider patients in a chronic lung disease, thus no recommendations exist in case of acute lung insufficiency and scleroderma of novel diagnosis. In addition, urgent lung transplant was performed which is a rare and almost unique report in scleroderma.
Changes in the text: we added the suggested references and improved the introduction section with the following text and with references 15 and 16: "However, few case reports describe the use of VV-ECMO in rapidly progressive interstitial lung disease (RPILD) arising as an acute complication of an autoimmune CTD." (See Page 4, line 75-77).

Comment 2: However, the authors refer to the reference 7 (Hoetzenecker et al.) while that particular study has excluded patients that were bridged to LTx in contrary to your case report. I would suggest replacing and rather referring to the last two above mentioned recent references on bridging with ECMO.
Reply 2: thank you. We did it.
Changes in the text: we removed the reference 7 and added the references suggested by the reviewer as reference 11 and 12.

Comment 3: The whole text needs to be revised for the English language and some weird expressions. Avoid capital letters within the text of abstract (VV ECMO). Please remove "Such scenario supports…" "VV ECMO helps to put…" "This means we applied tidal volume…" "We realized that VV ECMO…" "likely thanks to", "reason of death"
Reply 3: thank you.. We reviewed the English language as you suggested.
Changes in the text: we changed:
"such scenario supports…" with "this report supports" (see Page 2, line 45)
"VV ECMO helps to put" has been removed with the entire sentence, as you suggested in another point.
"we realized that VV-ECMO" was changed to "Consequently, the initial rescue V-V ECMO therapy became a potential bridge to lung transplant" (See Page 7, line 135-136).
We changed "this means we applied tidal volume.." with ". Mechanical ventilation was set in the ultra-protective modality; 3 ml/Kg IBW tidal volume" (See page 6, line 119-120)
We changed "likely thanks to" with "maybe because of.." (See Page 8, line 164-165)
We changed "Reason of death" with "this does not appear to impact long term survival (26)." (see page 10, line 220-221)

Comment 4: Line 43-46, please re-write, reference also missing.
Reply 4: thank you. We did it.
Changes in the text: we re-wrote lines 43-46 and added two references : "The progression of SSc is still characterized by a significant mortality ratio, ranging from 2.6 to 3.5 (2). The estimated survival is 75% at 5 years and 62.5% at 10 years from diagnosis and pulmonary involvement represents the main cause of death (3,4). Some degree of pulmonary involvement is seen in more than 80 percent of patients with SSc. The main clinical manifestations are Interstitial Lung Disease (ILD) (also called fibrosing alveolitis or pulmonary fibrosis) and pulmonary vascular disease, leading to pulmonary arterial hypertension (PAH). The incidence of ILD and PAH in patients with SSc pulmonary involvement is 70% and 10-12%, respectively (5)." (See Page 4, line 59-66).

Comment 5: Lines 50, 141-143 references missing
Reply 5: Thank you. Reference 26 already describes both patterns of recurrent interstitial lung disease and allograft rejection in transplanted lungs. Apart from this study, recurrence of usual interstitial pneumonia has not been reported in lung transplant recipients with idiopathic pulmonary fibrosis.
Changes in the text: no changes. :

Comment 6: Line 54, Why case series? Are there no case reports?
Reply 6: Thank you for your suggestion. We added references 15 and 16 as two case reports describing use of VV ECMO in acute onset of interstitial autoimmune disease.
Changes in the text: we rewrote line 54-56 with"Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO) has been used for years as a bridge to lung transplant in patients with end-stage restrictive lung disease secondary to scleroderma (11,12).However, few case reports describe the use of VV-ECMO in rapidly progressive interstitial lung disease (RPILD) arising as an acute complication of an autoimmune CTD." (See Page 4, line 72-74).

Comment 7: How long was the patient on immunosuppressive therapy? Can you provide dosing?
Reply 7: thank you for your suggestion. We checked in the patient record and we added some information about it.
Changes in the text: we replaced this part of the text : "The skin biopsy showed a positivity to anti-NMDA antibodies that lead to the diagnosis of systemic scleroderma. As a consequence, he started immunosuppressants and corticosteroids (cyclophosphamide and tacrolimus)" with the following: In September 2020 the patient underwent a skin biopsy that showed a positivity to anti-MDA5 antibodies which led to the diagnosis of Ssc.
At this stage, a combined immunosuppressive treatment regimen was initiated, with intravenous cyclophosphamide (6 mg/kg/die), oral tacrolimus (6mg/die) and methylprednisolone (1,5 mg/kg/day)." (See Page 5, line 96-100)
Moreover, we added the day of listing the patient in the lung transplant list and we specified that we submitted him the same therapy after the lung transplant with the following words "The results showed only a weak positivity three months after lung transplant, maybe because of the immunosuppressive protocol, similar to the one adopted in the pre-transplant period." (See Page 8,

line 164-166)

Comment 8: Line 74, Over which period of time the patient deteriorated? Since admission?
Reply 8: thank you for your suggestion, we answered your question adding some words in the text.
Changes in the text: we added "a few days after the hospital admission". (See Pag 5, line 101)

Comment 9: Line 77, pls re-write, use "contraindicated" rather than "impossibility"
Reply 9: thank you. We did it.
Changes in the text: we replaced the words " with impossibility to start an invasive mechanical ventilation" with "that contraindicated the invasive mechanical ventilation therapy". (See Page 6, linea 106-107).

Comment 10: Line 79-81, The readership is well aware of this. Either support with a reference and transfer to introduction or delete please.
Reply 10: thank you for your suggestion. We decided to delete line 79-81 because it is a concept already known.

Comment 11: PAC can be floated, but not ECMO cannula, pls replace
Reply 11: thank you for your correction. We replaced it.
Changes in the text: we replaced ``floated up to" with "placed to".

Comment 12: Line 88, So why the patient was not intubated in the first instance before implanting ECMO but is now? Why didn't the patient have chest drain if there was such significant bilateral PTx?
Reply 12: thank you for your comment.Since the patient had contemporary bilateral pneumothorax, pneumomediastinum and cervical emphysema, we thought that the positive pressure ventilation could have worsened dramatically the hemodynamic state. That's why we opted for awake VV ECMO cannulation, already discussed in literature. The thoracic surgeon evaluated the patient and decided not to put chest drain because it wouldn't have modified the clinical scenario significantly, due to the presence of severe pneumomediastinum and cervical emphysema.
Changes in the text: no changes.

Comment 13: Line 93, Which flow rate?
Reply 13: thank you for having underlined this mistake. Were removed "optimal patient blood flow
Changes in the text: we removed "optimal patient blood flow" in line 93.

Comment 14: …ranging between 89% and 90%, pls re-write as this is not a range
Reply 14: thank you. We replaced ranging with another more appropriate word.
Changes in the text: we replaced "raging" with "with a peripheral SpO_2 89% - 90%".

Comment 15: Line 95-98 needs to be re-written; you added a jugular cannula to achieve 10L flow but you obtained 5-6L, was there a need for additional cannula?!
Reply 15: thank you for your comment. We decided to remove technical details about ECMO running to simplify the case description.
Changes in the text: we removed "Having estimated a patient cardiac output of 10L/min, we added a 21-Fr cannula into the right internal jugular vein as a return cannula."
and "achieving 5-6 L/min of V-V ECMO flow and allowing a SpO_2 rise up to 98%."

Comment 16: Line 100-101, pls re-write and precisely describe ventilation parameters
Reply 16: thank you for your comment. We did it.
Changes in the text: we added the words in blankets " (Plateau Pressure > 40 cmH2O, Driving Pressure > 20 cmH2O cmH2O and Compliance of the Respiratory System < 15 cm/H20)" (see Page 7, line 132-133).

Comment 17: Line 105-107, pls re-write, was it MDT decision or anesthetic team made this decision?
Reply 17: thank you. We did it.
Changes in the text: we added the words ""the multidisciplinary lung transplant team of our hospital, which includes respiratory physician, thoracic and cardiac surgeons, anaesthesiologist, and intensivist care specialists, decided to list the patient for an urgent bilateral lung transplant on October 3, 2020." (See Page 7, line 138-141).

Comment 18: Line 113-116 needs to be re-written. Weaning of ECMO needs better explanation. Distal leg perfusion cannula is not placed to minimize risk of IRI… Why reference 7?
Reply 18: Thank you for your suggestion. We rewrote weaning from central to peripheral V-A ECMO at the end of the transplant procedure. We decided to keep Hoetzenecker K. et al reference because it explains our management in prolonged ECMO.
Changes in the text: we replaced "Weaning from central V-A ECMO was performed after having confirmed the ability of the new lungs to provide adequate oxygenation.
Central configuration was then switched to a peripheral femoro-femoral V-A ECMO configuration, with distal leg perfusion cannula, in order to minimize the risk of ischemia-reperfusion injury (IRI) and Primary Graft Dysfunction (PGD)" with
"At the end of the surgical procedure, the central V–A ECMO was switched to a peripheral femoro-femoral one with a semi-Seldinger technique, with the aim to off-load the patient's pulmonary circulation and right ventricle.The use of peripheral V-A ECMO after lung transplant is supported by Wien's group that demonstrated its role in reducing the incidence of PGD and right heart dysfunction in the early postoperative period (17).Adding a distal leg reperfusion cannula to the ECMO circuit in order to avoid peripheral ischemic complication is a routine practice in our local institution." (See Page 7, line 147-154)

Comment 19: I suggest to rephrase that your main concern was only the relapse after successful LTx
Reply 19: thank you for your suggestion. We added a comment in the discussion section.
Changes in the text: we added these words "For that reason, our main concern was the risk of relapse on transplanted lungs, but there wasn't any manifestation of relapse during the follow-up, probably because of immunosuppressive therapy". "Once the patient went through a successful bilateral lung transplant under the careful management of an experienced multidisciplinary team, there were further concerns regarding how the immune process may potentially continue to target autoantigens and fibrotic pathways on the new graft.To mitigate this risk as well as to prevent graft rejection, immunosuppressive therapy was initiated, with no clinical evidence of autoimmune disease relapse on the transplanted lungs at three months follow up." (See Page 10, line 212-218).

Comment 20: Pls start discussion with why you think this case report is original/not published before and re-write conclusion. I suggest removing the line 131-132.
Reply 20: thank you for your suggestion. We removed line 131-132 and we added some comments in the discussion.
Changes in the text: we added this words "There are no specific recommendations about management of RPILD and with this case report we can demonstrate that V-V ECMO may be used as a bridge to recovery or to transplant, and contributes to the experience of other authors" (See PAge 8, 178-180)
We rewrote conclusions adding these words: "Long-term follow-up is not available in our report, nor in other clinical experience (13,15,16,18). Long-term follow-up might be useful to further understand the outcomes of bilateral lung transplantation in cases of acute respiratory failure in RPILD secondary to SSc.Further studies with a long-term follow up are needed to support this practice and to assess the clinical benefits of lung transplant in autoimmune CTD complicated by RPLID." (See Page 10, line 227-233).

Comment 21: Line 133-134 needs to be re-written, overstatement
Reply 21: thank you for your suggestion. We decided to remove lines 133-134.
Changes in the text: we removed the words "There are no specific recommendations about management of RPILD and with this case report we can demonstrate that V-V ECMO may be used as a bridge to recovery or to transplant and contributes to the experience of other authors (13,14,16)." (See Page 8, linea 178-180)

Comment 22: Pls remove "V-V ECMO is not meant as a destination therapy"
Reply 22: thank you, we did it.
Changes in the text: we removed the words "V-V ECMO is not meant as a destination therapy, but only as a bridge to recovery or to transplant"

Comment 23: Line 144, "multiple reports" is supported with one reference, pls amend
Reply 23: thank you for your suggestion. We realized that "multiple reports" was

effectively not supported by enough references.
Changes in the text: we replace “multiple reports” with “De Cruz R. and Ross D.”

Reviewer C

Comment 1: Few clarifications will help: How long to wait before considering lung transplant in such cases? When do we know the lungs are irreparably damaged?
Reply 1: thank you for your comment. We added some comments in the discussion.
Changes in the text: we added these words “There are no recommendations for when to proceed with listing for transplantation in this scenario. According to the evidence reported in the literature, the mortality rate of short duration VV-ECMO (<14 days) is lower than the mortality rate of adults who require long duration VV- ECMO (> 14 days), because it is associated with potentially lethal complications like neurological injury, nosocomial infections, renal dysfunction and, eventually, multi organ failure (MOF) (25).The irreversibility of lung damage was evaluated with daily monitoring of the lung compliance and intrapulmonary shunt, estimated by blood gas analysis from the arterial and pulmonary artery catheter. Subsequent Chest X-Ray, showing parenchyma persistently infiltrated throughout the whole lung and the current diagnosis of autoimmune CTD further supported the diagnosis of irreversible lung damage.” (See Page 9, line 201-211).

Comment 2: The evaluation for transplant and listing seems to have been expedited..a little more detail on the process will be helpful.
Reply 2: thank you for your comment. We added some details in the case description.
Changes in the text: we added the words ““the multidisciplinary lung transplant team of our hospital, which includes respiratory physician, thoracic and cardiac surgeons, anaesthesiologist and intensivist care specialists, decided to list the patient for an urgent bilateral lung transplant on October 3, 2020.”
(see Page 8, line 138-141)

Comment 3: What is double filtration plasmapheresis? Please add few lines.
Reply 3: thank you for your comment. We added a few lines about this topic.
Changes in the text: we added the words “DFPP is a semi-selective blood purification technique derived from the plasma exchange modality that can rapidly remove the pathogenetic antibodies and immune complexes efficiently (14)..” (See Page 5, linea 81-83)

Comment 4: It will help to have X-rays showing the original cannula position with Fem-fem ecmo and after conversion to RIJ-bifemoral ecmo. Did the authors pull back the atrial cannula after the RIJ cannula was inserted to avoid recirculation? Also there were two drainage cannulae now, a 25F in the atrium and a 27F in the IVC...how much were they individually draining?
Reply 4: thank you for your comment. It is a pleasure to talk about these themes with you.

Unfortunately, cannula position was not evaluable because of widespread consolidation of both lungs. This is the reason why we are used to checking cannula position with transesophageal ultrasound, all the more reason during position of RIJ cannula.
We couldn't estimate how much 25F and 27F cannulae drained. Otherwise, this double drainage cannulae allowed higher ECMO flow.
Changes in the text: we added these words " checked by transesophageal echocardiography" and "Recirculation was appropriately excluded with blood gas analysis withdrawal in VV-ECMO out-let and in-let lines". (See Page 6, line 122-126).

Comment 5: How do you estimate the shunt fraction?
Reply 5: thank you for your comment. We are used to monitor the ECMO patient with a pulmonary artery catheter, that allows tn evaluate shunt fraction and the contribution of the natural lung to VO 2 by simply drawing blood gases from the arterial and pulmonary artery catheter.
Changes in the text: we added these words "estimated by blood gas analysis from the arterial and pulmonary artery catheter." (See Page 9, line 208-209).

Comment 6: Did the patient participate in physical therapy prior to listing? Is that a pre-requisite for listing at your center?
Reply 6: thank you for your comment. The patient didn't partecipate in physical therapy because he was intubated and under sedation after V-V ECMO placement. In our Centre patients undergo physical therapy if they are responsive and able to collaborate.
Changes in the text: no changes.

Comment 7: How was the VA ECMO decannulated? Surgically or percutaneous?
Reply 7: thank you for your comment. V-A ECMO peripheral cannulae was put with the semi-Seldinger technique and the removal process is the same of fullp ercutaneus approach.
Change in the text: We added the words " with a semi-Seldinger technique" (See Page 7, line 148)

Comment 8: If figure 2-it would help to point out the cannulae- drainage and return. The resolution of the X-ray could be better.
Reply 8: thank you for your comment. Unfortunately, the resolution of the figure-2 X-ray is the best that we can obtain. It is impossible to identify cannulae tips because of the complete bilateral consolidation of both lungs.
Changes in the text: no changes.

Reviewer D

Comment: There is nothing fundamentally new in your case report:
There are numerous articles evaluating lung transplantation in auto-immun disease in general and in scleroderma in particular - overall about 40. The majority of the newer papers has very good data about long term survival, 5 or more years.

You unfortunately only report 3 months, which does not add anything to our current body of knowledge.
ECMO as a bridge to lung transplantation in areas with an urgent allocation scheme is more than 10 years old. Putting someone with auto-immune disease on ECMO brings with it no other or new challenges than those we face on d regular basis.
Again, I am sorry for all the work you have put into writing this paper but it does not add anything to the literature that has not been reported several times.
Reply: thank you for your comment, but unfortunately we disagree on some things. It is correct that there are multiple articles on lung transplant in scleroderma but just a few in an acute setting. Moreover, fulminant ARDS in previously unknown scleroderma is a rare condition and just a few cases report successful treatment with lung transplant after VV-ECMO. In our opinion, the article may be interesting and helpful in such a rare situation. Nevertheless, as you mention, the follow-up is short, ECMO as bridge to lung transplant is becoming frequent and lifesaving and multiple nations have urgent lists for end-stage patients.