Respiratory Medicine Case Reports 36 (2022) 101595

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case Report

Autopsy findings of a patient with severe COVID-19 treated with long-term extracorporeal membrane oxygenation

Keigo Sekihara [a], Tatsuki Uemura [a,c], Tatsuya Okamoto [a,*], Mayu Sugiyama [a], Kaoru Yoshikawa [a], Koichiro Tomiyama [a,c], Takatoshi Shibasaki [a,c], Fumito Kato [a,c], Hideki Miyazaki [b], Toru Igari [b], Akio Kimura [a,c]

[a] Department of Intensive Care Medicine, Center Hospital of the National Center for Global Health and Medicine, Shinjuku, Tokyo, Japan
[b] Pathology Division of Clinical Laboratory, Center Hospital of the National Center for Global Health and Medicine, Shinjuku, Tokyo, Japan
[c] Department of Emergency Medicine and Critical Care, Center Hospital of the National Center for Global Health and Medicine, Shinjuku, Tokyo, Japan

ARTICLE INFO

Keywords:
Autopsy pathology
COVID-19
Diffuse alveolar damage
Extracorporeal membrane oxygenation
Pulmonary hemorrhage
SARS-CoV-2

ABSTRACT

Extracorporeal membrane oxygenation (ECMO) therapy in patients with coronavirus disease 2019 (COVID-19) has a low frequency of use, and thus pathological findings in such patients are valuable. In this case report, a 62-year-old man with a history of hypertension presented with a runny nose. After an at-home COVID-19 positive test, he developed dyspnea and fever. Once admitted to our hospital, his oxygenation worsened, and ECMO was initiated. He died from respiratory failure 69 days after ECMO induction. Macroscopically, the lungs gained mass, were partially consolidated, and were airless. Histological analysis revealed diffuse bronchial epithelial metaplasia and adenoid metaplasia in the alveolar epithelium. Although the lung parenchyma was partially preserved, there was organizing and fibrosis that filled pulmonary alveolus due to COVID-19 and changes resulting from disuse and long-term ECMO.

List of abbreviations

COVID-19	coronavirus disease 2019
CT	computed tomography
ECMO	extracorporeal membrane oxygenation
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
VILI	Ventilator-induced lung injury

1. Introduction

The number of deaths due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has increased worldwide. Full

* Corresponding author. Department of Intensive Care Medicine, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku, Tokyo, 162-8655, Japan.
E-mail address: taokamoto@hosp.ncgm.go.jp (T. Okamoto).

https://doi.org/10.1016/j.rmcr.2022.101595
Received 7 December 2021; Received in revised form 13 January 2022; Accepted 24 January 2022
Available online 29 January 2022

pathological examination upon autopsy has significant value for understanding the pathophysiology of a disease, especially when the knowledge about an emerging disorder is limited [1–3]. In the current case report, the pathological findings of a severe COVID-19 patient treated with extracorporeal membrane oxygenation (ECMO) are shared.

The validity of ECMO for severe respiratory failure has been demonstrated previously for H1N1 influenza [4]; hence, ECMO is also recommended for eligible patients with SARS-CoV-2 [5,6]. However, the frequency of ECMO support use is relatively low at ~3% in severe COVID-19 cases with the restoration of adequate oxygenation [7], and its induction has remained geographically restricted to a few specialized centers. Thus, pathological findings from patients for which ECMO was induced can be recorded in a few cases, making autopsy findings for those treated with ECMO valuable knowledge.

2. Case report

A 62-year-old non-smoking man with a history of hypertension (HTN) presented with complaints of a runny nose. The patient was diagnosed with COVID-19 after a polymerase chain reaction test. After he complained of dyspnea and fever during his stay at home, the patient was transported to our hospital. Chest radiography revealed pneumonia in the bilateral lung fields; and chest computed tomography (CT) revealed ground-glass opacity, patch consolidation, and tractional bronchodilation (Fig. 1).

ECMO, extracorporeal membrane oxygenation; RA, right atrium; SVC, superior vena cava.

The patient was then intubated and treated with Remdesivir 200 mg (first day only), 100 mg (2nd–10th day), heparin 15,000–20,000 units, Tocilizumab 600 mg (administered on the first day only), and dexamethasone 6.6 mg per day. His oxygenation levels worsened despite on mechanical ventilation, and ECMO was inducted seven days after intubation. During ECMO therapy, the artificial respirator was set as follows: assist control, respiratory rate 10–15 per min, driving pressure 5–10 cm H_2O, positive end-expiratory pressure 10–15 cm H_2O, and a fraction of inspiratory oxygen(i.e., 40%). The lung rest setting could not be expanded

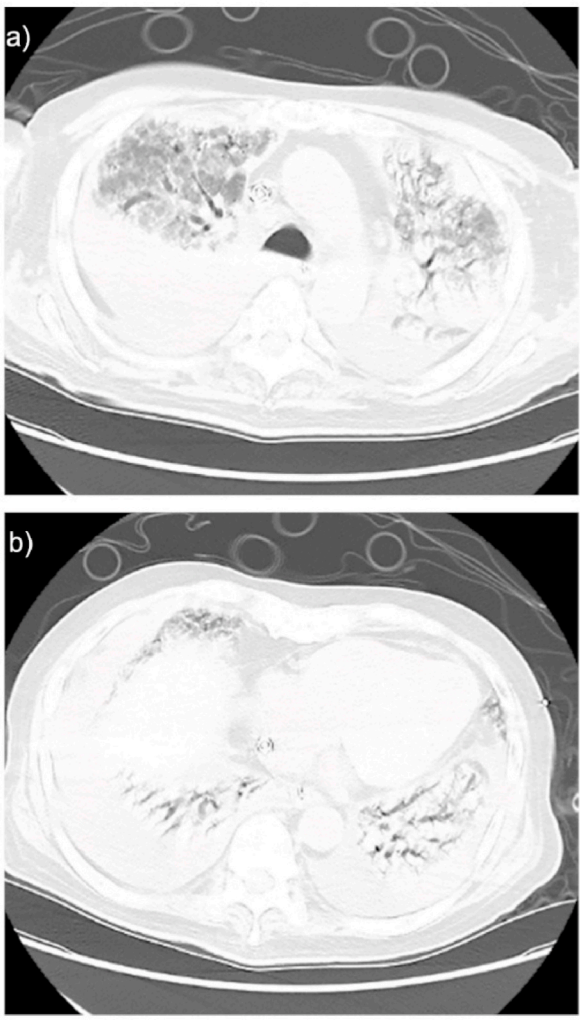

Fig. 1. a) Chest CT scan showing ground-glass opacity, air bronchogram, patchy consolidation in the bilateral upper lobes, bilateral pleural effusion, and the ECMO catheter in the SVC. b) Chest CT scan demonstrating atelectasis, organizing, bilateral air bronchogram, and the ECMO catheter in the RA.

adequately due to fibrositis due from the SARS-CoV-2 infection (Fig. 2). The patient died from respiratory failure 69 days after ECMO induction.

An autopsy was conducted 19h after death, excluding the brain. Macroscopically, the lungs gained weight (left, 720 g; right, 910 g). They were partially consolidated, airless, and showed a hematoma in the right middle lobe. The cut surface showed diffuse white changes in each lobule that were dominant in the lower lobes, and there was a clear pleural effusion in the bilateral thoracic cavity (left, 500 ml; right, 750 ml).

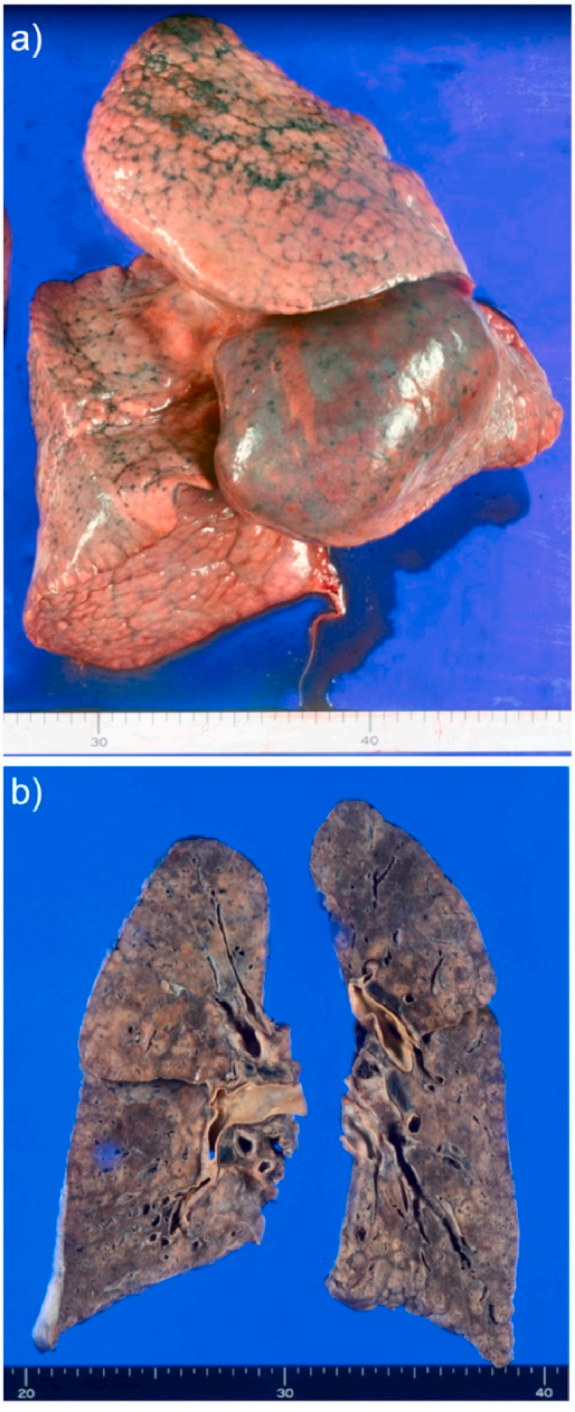

Fig. 2. Representative images of the macroscopic findings. a) A cystic lesion and a hemorrhage in the right middle lobe (right lung before formalin fixation) are seen. b) White centrilobular organization is noted markedly in the bilateral lower lobes (cut surface of the lungs after formalin fixation).

Histological analysis revealed diffuse bronchial epithelial metaplasia and adenoid metaplasia in the alveolar epithelium. Hyperemia, hyperplasia, and dilation of the capillary blood vessels in the interalveolar septum were also demonstrated. These lesions showed changes caused by long-term ECMO therapy. Although organizing and fibrosis that filled the pulmonary alveoli were observed in some places, the air space was maintained in most parts of the upper lobes (Fig. 3). Macrophages, neutrophils, and bleeding were also observed in the interalveolar space. The patient also developed bacterial pneumonia as a complication.

EVG, elastica van Gieson; HE, Hematoxylin and Eosin.

3. Discussion

This case study reports the autopsy of a 62-year-old man with severe COVID-19 who underwent long-term ECMO, which revealed histopathologic lesions and disuse changes.

The severity of SARS-CoV-2 varies from case to case, from asymptomatic to deceased, and is widely known to cause severe respiratory failure, which is the leading cause of death in COVID-19 patients. Anti-viral drugs, immunosuppressive therapy, and anticoagulation therapy have proven effective [8–11]. Under this multidrug regimen, mechanical ventilation and ECMO are central to respiratory management in severe cases.

In various levels of COVID-19 progression and severity, diffuse alveolar damage (DAD) and organizing are major pathological features in patients with COVID-19 infection [2]. In this case, histopathologic lesions that were attributed to the COVID-19 were limited, and the predominant finding was disuse changes due to ECMO. We did reveal DAD in some portions of the lungs and noted organizing, especially in the lower lobes. However, the lung tissue was partly maintained in both upper lobes. The treatment effect of

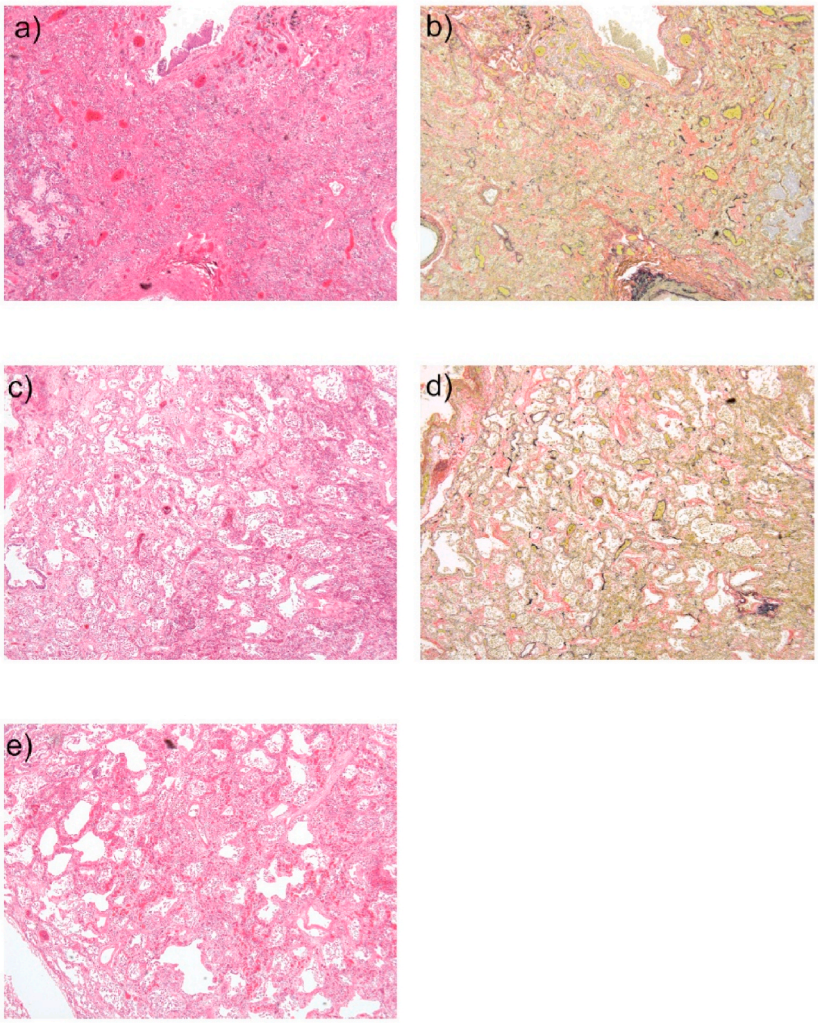

Fig. 3. a). Representative images of the histological findings a), b) organizing and fibrosis that filled pulmonary alveolus in the lower lobe; c), d) maintained air space and pulmonary alveolus in the upper lobe,
a) HE stain, 40× magnification), b) EVG stain, 40× magnification, c) HE stain, 40× magnification, d) EVG stain, 40× magnification, e) Congestion and disuse changes in the lower lobe (HE stain, 40× magnification).

ECMO is a result of many factors, such as oxygenation, to avoid acidosis from the accumulation of carbon dioxide. One of the most important factors in this treatment is avoiding ventilator-induced lung injury (VILI). A previous report demonstrated that low driving pressure decreases VILI and preserves lung tissues [12]. In addition, improved survival was noted in patients with severe, but potentially reversible, respiratory failure [13]. For this case, we considered that the preserved lung parenchyma in the upper lobes was a treatment effect of ECMO.

The most common complication of ECMO is hemorrhage [4]. Histopathologic findings in the lungs treated with ECMO are also often reported, and the incidence of pulmonary hemorrhage is 63.2% [14]. In our case, an old hemorrhage was observed in the form of a pulmonary cyst, but no other histological changes were observed in either the lungs or the gastrointestinal mucous membrane. Intracranial hemorrhage has also been reported as a cause of death in patients receiving ECMO [15]; although we excluded the brain at autopsy, the CT scan for this patient demonstrated no intracranial hemorrhage.

Despite the induction of ECMO, the cause of death in this patient was respiratory failure resulting from composite factors that produced organizing due to COVID-19, disuse changes due to long-term ECMO, and the complication of bacterial pneumonia. ECMO is effective invasive oxygenation, but only supports therapy for respiratory failure. A treatment regimen for patients with severe COVID-19 is needed. Since our patients were unvaccinated, it also underlines the need for widespread vaccinations in the community.

4. Conclusion

Although histological changes in this patient were similar to conventional COVID-19 cases, we found preserved lung parenchyma in parts of the lung, which was a treatment effect induced by ECMO.

Funding

This study was funded by the International Health Research and Development Fund, Ministry of Health, Labor and Welfare, Japan (No. 20A01).

Author contributions

Keigo Sekihara, Tatsuki Uemura, Tatsuya Okamoto, Mayu Sugiyama, Kaoru Yoshikawa, and Akio Kimura: Conception and design of the study.

Keigo Sekihara, Tatsuki Uemura, Takatoshi Shibasaki, Fumito Kato, Koichiro Tomiyama, and Tatsuya Okamoto: Acquisition and analysis of data.

Keigo Sekihara, Tatsuki Uemura, Hideki Miyazaki, and Toru Igari: drafting the manuscript or figures.

All authors: revision of the manuscript, approval of the manuscript for publication, and agreement to be held accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing interest

None.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

References

[1] T. Adachi, J.M. Chong, N. Nakajima, M. Sano, J. Yamazaki, I. Miyamoto, H. Nishioka, H. Akita, Y. Sato, M. Kataoka, H. Katano, M. Tobiume, T. Sekizuka, K. Itokawa, M. Kuroda, T. Suzuki, Clinicopathologic and immunohistochemical findings from autopsy of patient with COVID-19, Japan, Emerg, Inf. Disp. 26 (2020) 2157–2161, https://doi.org/10.3201/eid2609.201353.

[2] R.B. Martines, J.M. Ritter, E. Matkovic, J. Gary, B.C. Bollweg, H. Bullock, C.S. Goldsmith, L. Silva-Flannery, J.N. Seixas, S. Reagan-Steiner, T. Uyeki, A. Denison, J. Bhatnagar, W.J. Shieh, S.R. Zaki, COVID-19 Pathology Working Group, Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States, Emerg, Inf. Disp. 26 (2020) 2005–2015, https://doi.org/10.3201/eid2609.202095.

[3] K. Okudela, H. Hayashi, Y. Yoshimura, H. Sasaki, H. Horiuchi, N. Miyata, N. Tachikawa, Y. Tsuchiya, H. Mitsui, K. Ohashi, A Japanese case of COVID-19: an autopsy report, Pathol. Int. 70 (2020) 820–824, https://doi.org/10.1111/pin.13002.

[4] F.C. Chow, B.L. Edlow, M.P. Frosch, W.A. Copen, D.M. Greer, Outcome in patients with H1N1 influenza and cerebrovascular injury treated with extracorporeal membrane oxygenation, Neurocritical Care 15 (2011) 156–160, https://doi.org/10.1007/s12028-011-9534-7.

[5] K. Ramanathan, D. Antognini, A. Combes, M. Paden, B. Zakhary, M. Ogino, G. MacLaren, D. Brodie, K. Shekar, Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases, Lancet Respir. Med. 8 (2020) 518–526, https://doi.org/10.1016/S2213-2600(20)30121-1.

[6] B.M. Henry, COVID-19, ECMO, and lymphopenia: a word of caution, Lancet Respir. Med. 8 (2020) e24, https://doi.org/10.1016/S2213-2600(20)30119-3.

[7] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA 323 (2020) 1061–1069, https://doi.org/10.1001/jama.2020.1585.

[8] J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, E. Nicastri, Lescure, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, T. Flanigan, Compassionate use of Remdesivir for patients with severe covid-19, N. Engl. J. Med. 382 (24) (2020) 2327–2336.

[9] R.M. Johnson, J.M. Vinetz, Dexamethasone in the management of covid -19, BMJ 370 (2020) m2648, https://doi.org/10.1136/bmj.m2648.

[10] J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A.S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M.D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.D. Halvorsen, T.K. Thurber, Z. Dagher, A. Scherer, R.S. Wallwork, A.Y. Kim, S. Schoenfeld, P. Sen, T.G. Neilan, C.A. Perugino, S.H. Unizony, D.S. Collier, M.A. Matza, J.M. Yinh, K.A. Bowman, E. Meyerowitz, A. Zafar, Z.D. Drobni, M.B. Bolster, M. Kohler, K.M. D'Silva, J. Dau, M.M. Lockwood, C. Cubbison, B.N. Weber, M.K. Mansour, BACC bay Tocilizumab trial investigators, efficacy of tocilizumab in patients hospitalized with covid-19, N. Engl. J. Med. 383 (2020) 2333–2344, https://doi.org/10.1056/NEJMoa2028836.

[11] N. Tang, H. Bai, X. Chen, J. Gong, D. Li, Z. Sun, Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, J. Thromb. Haemostasis 18 (2020) 1094–1099, https://doi.org/10.1111/jth.14817.

[12] J. Araos, L. Alegria, P. Garcia, P. Cruces, D. Soto, B. Erranz, M. Amthauer, T. Salomon, T. Medina, F. Rodriguez, P. Ayala, G.R. Borzone, M. Meneses, F. Damiani, J. Retamal, R. Cornejo, G. Bugedo, A. Bruhn, Near-apneic ventilation decreases lung injury and fibroproliferation in an acute respiratory distress syndrome model with extracorporeal membrane oxygenation, Am. J. Respir. Crit. Care Med. 199 (2019) 603–612, https://doi.org/10.1164/rccm.201805-0869OC.

[13] G.J. Peek, M. Mugford, R. Tiruvoipati, A. Wilson, E. Allen, M.M. Thalanany, C.L. Hibbert, A. Truesdale, F. Clemens, N. Cooper, R.K. Firmin, D. Elbourne, CESAR trial collaboration, Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (Cesar): a multicentre randomised controlled trial, Lancet 374 (2009) 1351–1363, https://doi.org/10.1016/S0140-6736(09)61069-2.

[14] H.E. Lee, E.S. Yi, J.T. Rabatin, J.K. Bohman, A.C. Roden, Histopathologic findings in lungs of patients treated with extracorporeal membrane oxygenation, Chest 153 (2018) 825–833, https://doi.org/10.1016/j.chest.2017.12.007.

[15] Y.A. Cavayas, L. Del Sorbo, E. Fan, Intracranial hemorrhage in adults on ECMO, Perfusion 33 (1_suppl) (2018) 42–50, https://doi.org/10.1177/0267659118766435.