RAPID COMMUNICATION

SARS-CoV-2 Viral Load Assessment in Lung Transplantation

Rene NOVYSEDLAK[1], Jiri VACHTENHEIM Jr.[1], Ilja STRIZ[2], Ondrej VIKLICKY[3], Robert LISCHKE[1], Zuzana STRIZOVA[4]

[1]Third Department of Surgery, Prague Lung Transplant Program, First Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic, [2]Department of Immunology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, [3]Department of Nephrology, Transplant Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, [4]Department of Immunology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

Received July 14, 2021
Accepted August 26, 2021

Summary

In the era of COVID-19 pandemic, organ transplantation programs were facing serious challenges. The lung transplantation donor pool was extremely limited and SARS-CoV-2 viral load assessment has become a crucial part of selecting an optimal organ donor. Since COVID-19 is a respiratory disease, the viral load is thought to be more important in lung transplantations as compared to other solid organ transplantations. We present two challenging cases of potential lung donors with a questionable COVID-19 status. Based on these cases, we suggest that the cycle threshold (Ct) value should always be requested from the laboratory and the decision whether to proceed with transplantation should be made upon complex evaluation of diverse criteria, including the nasopharyngeal swab and bronchoalveolar lavage PCR results, the Ct value, imaging findings and the medical history. However, as the presence of viral RNA does not ensure infectivity, it is still to be clarified which Ct values are associated with the viral viability. Anti-SARS-CoV-2 IgA antibodies may support the diagnosis and moreover, novel methods, such as quantifying SARS-CoV-2 nucleocapsid antigen in serum may provide important answers in organ transplantations and donor selections.

Key words

COVID-19 • Lung transplantation • Organ donor • PCR • Cycle threshold

Corresponding author

Z. Strizova, Department of Immunology, Second Faculty of Medicine, Charles University and University Hospital Motol, V Uvalu 84, 150 06 Praha 5, Czech Republic. E-mail: zuzana.strizova@fnmotol.cz

Coronavirus disease 2019 (COVID-19) pandemic has become one of the greatest challenges in the recent history (Lacina *et al.* 2021, Hubacek *et al.* 2021, Paces *et al*. 2020). The disease outbreak has impacted the entire society with one of the most influenced area being the healthcare (Huang *et al*. 2021).

Due to an extremely high transmissibility and a high mortality of COVID-19, especially among immunocompromised patients, both diagnostic and therapeutic processes have significantly changed (Paces *et al*. 2020, Patt *et al.* 2020, Sica *et al.* 2021, Khairallah *et al.* 2021, Vasku 2020). In order to manage this unprecedented situation, intensive care units, as well as standard hospital wards and ambulatory care practices, were accordingly reshaped to provide the best protection against COVID-19 transmission and to allow gaining a control over the COVID-19 (Dzupova *et al.* 2021, Baccolini *et al.* 2021).

Nonetheless, while the management of the COVID-19 dominated the diagnostic and therapeutic landscape in most European countries, other medical areas were negatively altered (Patt *et al.* 2020, Sica *et al.*

2021, Khairallah *et al.* 2021, Dzupova *et al.* 2021, Allam *et al.* 2020).

In the era of COVID-19 pandemic, organ transplantation programs faced serious challenges (Azzi *et al.* 2021, Esagian *et al.* 2020, DeFilippis *et al.* 2020). The lung transplantation donor pool was extremely limited and novel guidelines for the management of organ donors and recipients had to be created (Azzi *et al.* 2021, Keller *et al.* 2020).

The COVID-19 mortality among transplant recipients was found to be substantially high and thus, a great effort is still being made to search for SARS-CoV-2 in both organ donors and recipients (Lieberman *et al.* 2020). Currently, all potential organ recipients on the transplant waiting list are advised to undergo vaccination against the COVID-19 and are screened for the COVID-19 infection prior to transplantation (Scharringa *et al.* 2021). Vaccination against the COVID-19 is also recommended in organ recipients after the transplantation despite the fact that several studies already indicated the impairment of the anti-SARS-CoV-2 specific immunity in solid organ transplant recipients (Shostak *et al.* 2021, Havlin *et al.* 2021). In fact, mRNA vaccines were found to elicit only limited antibody responses in lung transplant recipients but contrarily, displayed a capacity to promote the induction of anti-SARS-CoV-2 reactive T cells (Shostak *et al.* 2021, Havlin *et al.* 2021).

Still, there are many issues that accompany the SARS-CoV-2 viral load assessment in organ donors. For instance, various studies already reported cases of unclear COVID-19 status in individuals that required a highly personalized and careful evaluation of their infectivity based on multiple criteria (Lieberman *et al.* 2020, Oran *et al.* 2021, Messika *et al.* 2021, Amor *et al*. 2021, Rao *et al.* 2020, Theodore *et al*. 2021, Miller *et al*. 2021, Fisher *et al*. 2021).

In this report, we present two challenging cases of potential lung donors with a questionable COVID-19 status, Figure 1.

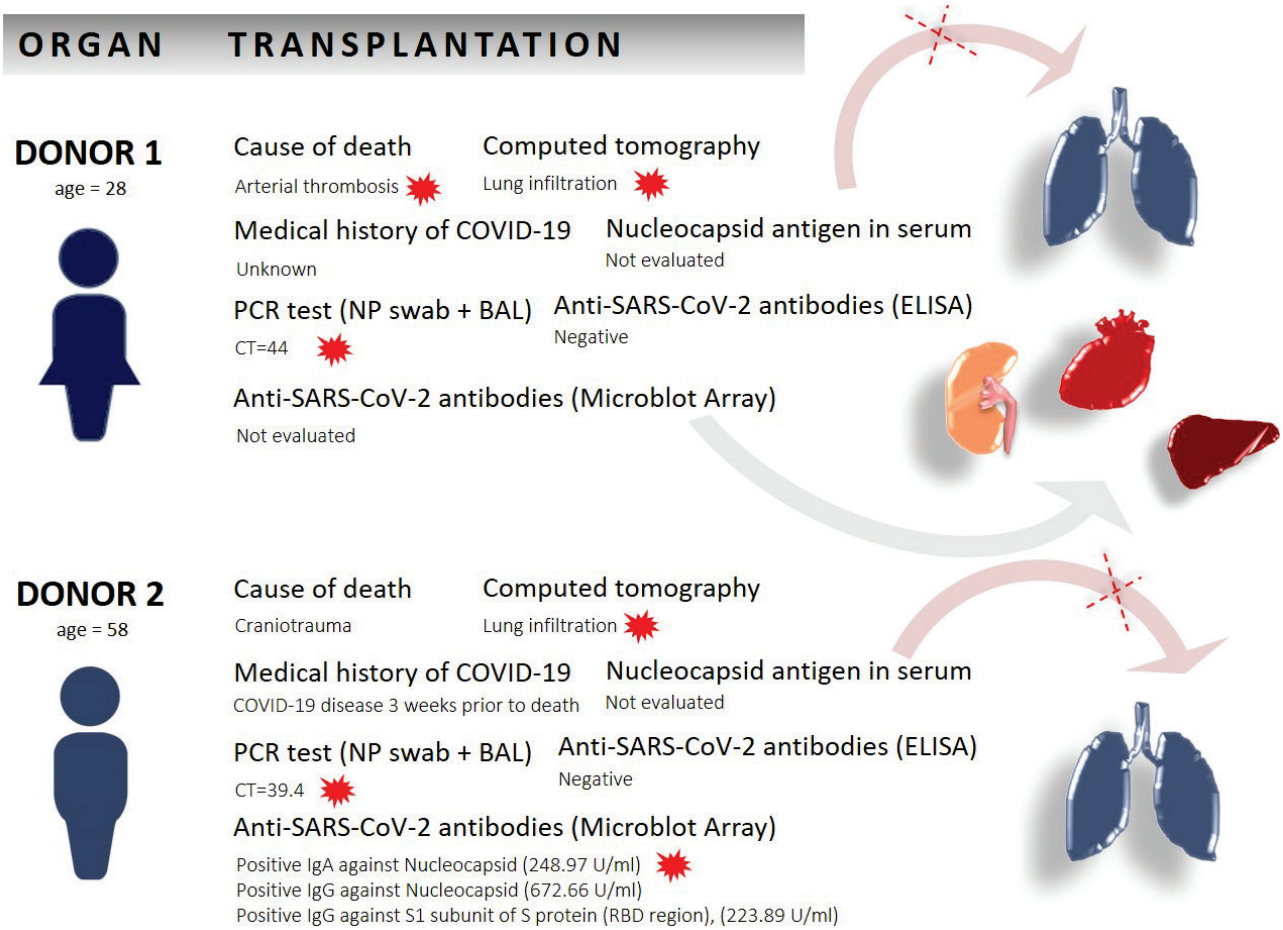

Fig. 1. Two donors and relevant factors associated with the clinical decision-making in relation to SARS-CoV-2 viral load and organ transplantation. Red marks label the factors that served as the exclusion criteria for lung transplantation.

The first donor was a young 28-years old female that died due to a thrombosis of basilar artery. This donor was presented as SARS-CoV-2 PCR positive at the primary Institution but came out PCR negative one day later at another Institution. Her organs were being considered for transplantation.

According to the generally accepted recommendations, bronchoalveolar lavage (BAL) should be examined in patients with suspected COVID-19 infection after a negative nasopharyngeal (NP) swab (Theodore *et al*. 2021, Gao *et al.* 2021). In our case, two consecutive PCR tests performed on BAL were negative, as well as the anti-SARS-CoV-2 antibodies that were retrospectively examined. To assess the level of positivity of the first PCR, we have requested the cycle threshold (Ct) count from the primary Institution. The Ct was 44 and, in most cases, Ct above 40 is considered negative (Falasca *et al.* 2020). Nevertheless, PCR assays are highly sensitive and allow a detection of an extremely low viral load (Oran *et al.* 2021, Messika *et al.* 2021). Therefore, in the process of decision-making whether to transplant, this became an issue. Also, the *computed tomography (CT)* revealed non-specific lung infiltration that could imply viral affection. Based on these findings, the lungs were not transplanted while the heart, the liver and the kidney transplantations were performed.

The second case was a 58-years-old male who died due to a craniotrauma that had a recent medical history of COVID-19 disease. This donor was tested SARS-CoV-2 PCR positive with the Ct 38 two days before the admission and the Ct 39.4 at the day of the planned transplantation. To obtain more data, we have retrospectively examined the antibodies by a microblot-array and found positive IgG against the *RBD region* and against the nucleocapsid, and positive IgA against the nucleocapsid (248.9 U/ml). CT revealed pleural effusion with associated lung parenchyma abnormalities and thus, the lung transplantation was not carried out.

SARS-CoV-2 viral load assessment is a crucial part of selecting an optimal organ donor (Lieberman *et al.* 2020). Since COVID-19 is a respiratory disease, the viral load may be more important in lung transplantations as compared to other solid organ transplantations (Messika *et al.* 2021). General criteria for accepting/declining lungs remain controversial and to date, there is still a significant proportion of possible donor lungs that are declined due to parenchyma abnormalities, such as pulmonary arterial thrombosis, pulmonary infarction, bronchopneumonia, and other findings (Verleden *et al.* 2017).

CT examination was proposed as a simple and valuable tool to decide whether to accept or decline donor lungs. Yet, there is no evidence that lungs with CT alterations could not be transplanted (Verleden *et al.* 2017).

In the era of COVID-19, accepting or declining donor organs for transplantations has become extremely challenging and especially the quality of lung allografts has raised serious concerns (Azzi *et al.* 2021, Keller *et al.* 2020).

While the COVID-19 pandemic has led to an increase of patients dying while on transplant waiting list, the risk of severe illness and death from COVID-19 in transplant recipients seems to outweigh the risk of donor organ shortage (Miller *et al*. 2021, Fisher *et al*. 2021).

PCR testing allow prompt and accurate detection of SARS-CoV-2, however, the information about the positivity/negativity alone may not be sufficiently sensitive to discriminate acceptable and nonacceptable lungs (Lanser *et al.* 2021).

Based on our previous experiences, we suggest that in unclear cases, the Ct value should always be requested and the decision should be made upon complex evaluation of diverse criteria, including the NP swab and BAL PCR results, the Ct value, imaging findings and medical history, Figure 2. To note, it is still to be clarified which Ct values are associated with the viral viability. Anti-SARS-CoV-2 IgA antibodies may support the diagnosis and moreover, novel methods, such as quantifying SARS-CoV-2 nucleocapsid antigen in the serum may provide important answers in organ transplantations and donor selections (Ogata *et al.* 2020).

Conflict of Interest

There is no conflict of interest.

Acknowledgements

The study was not supported by external funding.

Abbreviations

BAL – bronchoalveolar lavage, COVID-19 – coronavirus disease 2019, CT – computed tomography, Ct – cycle threshold, Ig – immunoglobulin, NP – nasopharyngeal, PCR – polymerase chain reaction, RBD – receptor binding domain, RNA – ribonucleic acid, SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2, SOT – solid organ transplant.

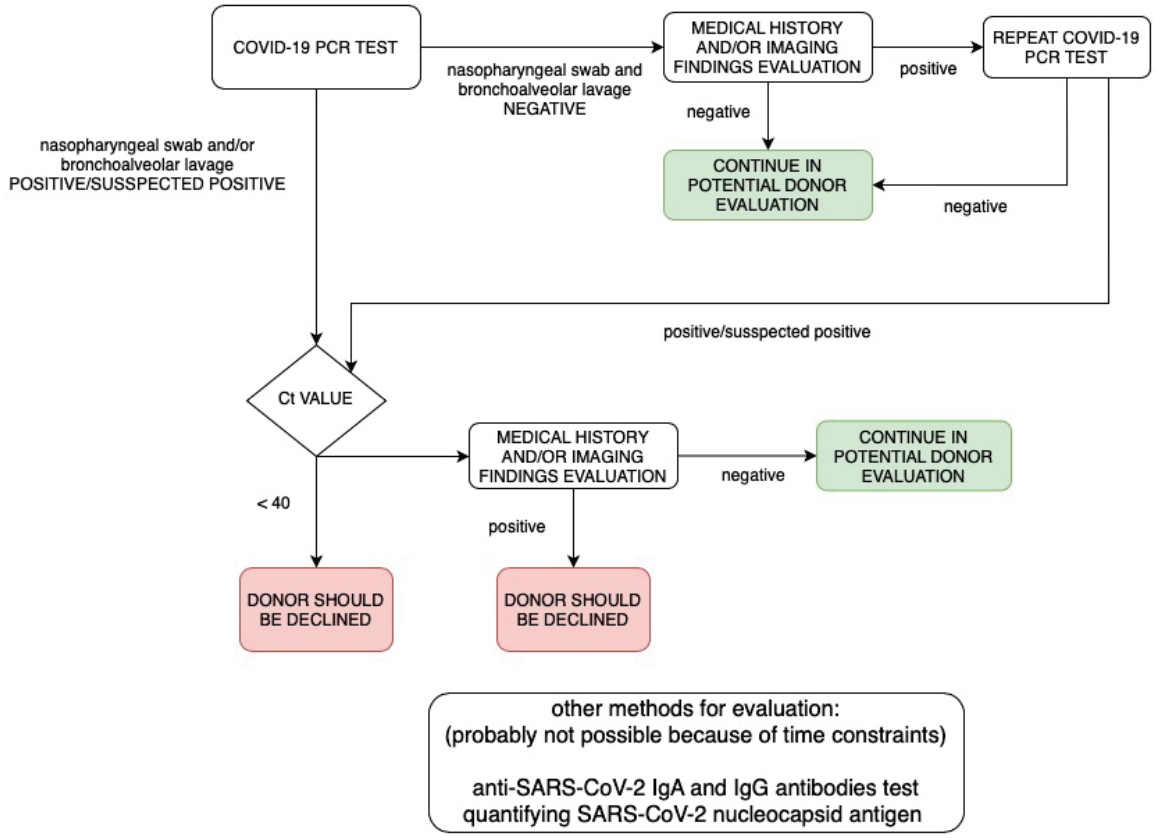

Fig. 2. Diagnostic algorithm for the evaluation of COVID-19 status in organ donor in lung transplantation.

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