

The critical impact of the COVID-19 pandemic on liver transplantation

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ABSTRACT

Health care systems worldwide were proven unprepared when faced with the COVID-19 pandemic and its inefaceable effect. Facing COVID-19 complications led to the implementation of a great number of measures. The impact on solid organ transplantation and especially liver transplantations (LT) was noteworthy. Repositioning of personnel, lack of non-COVID ICU beds and suspension of operation for several departments are only a few of the factors contributing to the decrease of LTs performed, during the first and second waves of the pandemic. The restricted number of donors negatively affected the waiting lists. Scientific societies published new guidelines in an effort to widen the pool of donors. The aim of our study was to depict the major impact of COVID-19 on the liver transplantations performed worldwide and in Greece, taking into consideration both patients and health care systems.

Key Words: *Liver transplantation; end stage liver disease; Covid-19; pandemic; waiting list*

INTRODUCTION

The COVID-19 pandemic began at the end of 2019 in China and swiftly became a worldwide problem, affecting millions of people, thus requiring the immediate response of health care systems for diagnosis, treatment and prevention strategies. As an example, the employment of COVID-19-free surgical pathways, where surgery and postoperative care are delivered in areas without COVID-19 patients, provided a solution associated with lower rates of pulmonary complications [1-3]. COVID-19 has critically affected healthcare systems worldwide in a catalytic way, resulting in major alterations in transplantation of solid organs and especially liver transplantation (LT) [4]. The

multiple consequences of a healthcare crisis as such should be considered in order to note its sweeping effect [5].

By way of illustration, the dramatic reduction of non-COVID intensive care unit (ICU) beds led to a consequential depletion of prospective deceased organ donors [6]. It is well known that ICUs constitute the main source of organ donors, in most cases brain dead patients with well-preserved organ function [7]. Several institutions and departments have suspended their operation, due to understaffing [8,9]. Blood donation departments came across the pandemic-related inability to provide blood products [10]. The puzzle is completed by the unsuccessful follow-up of patients with end stage liver disease, in need of LT, which leads to further complications.

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IMPACT OF COVID-19 ON THE NUMBER OF PERFORMED LIVER TRANSPLANTATIONS

Searching the international bibliography and formal statistical data concerning LT, the negative effects of the COVID-19 outbreak become easily evident. In particular, during the first and second surge of the pandemic, a

universal decrease in LTs was noted, exceeding a 10% in deceased donors and 12% in living donor transplants [11].

In order to explain such a negative impact of the COVID-19 pandemic on LT, some facts should be initially highlighted. Worldwide, the vast majority of liver transplantation activity is performed in the public health sector. Unfortunately, these public hospitals were also responsible for dealing with COVID-19 pandemic, in most of the affected countries [12]. Additionally, many health care physicians (including surgeons, anesthesiologists, hepatologists or intensivists), as well as nursing staff, normally engaged in LT had been unavoidably repositioned or directed towards management of COVID-19 patients [13]. This condition subsequently inhibited or even postponed their activity in several LT fields, such as donor identification, organ allocation and transplantation surgery.

LT displayed great dissimilarities in regard to the impact and recovery from place to place. For instance, the eastern Mediterranean has been greatly affected during this period with a 42% decrease in LTs. In the areas of south-east Asia and India, percentages reached 29% and 31% respectively. The decrease was approximately 15% in the rest of Europe and even lower in America (about 5%) [11]. According to the Global Observatory on Donation and Transplantation (GODT), the decrease in LTs across Europe had been impressive during 2018-2021 [14]. In particular, while during 2019, 8963 LTs by deceased donors were conducted, the number decreased to 7590 and 6041 during 2020 and 2021 respectively. Simultaneously, LT in Eurotransplant (a collaboration of eight European countries for transnational disposal of allografts) faced a downward tendency following the pandemic waves. In 2021, 1463 transplants were conducted, while the previous two years the numbers were 1420 and 1536 for the years 2020 and 2019 respectively [6,15]. Rationally, the observed reduction in LT activities among most countries was pronounced during the lockdown periods. In reference to France, a 22% decrease in the number of nationally performed LTs was recorded within 2020 (from 556 in 2019 to 435 in 2020) [13]. On the other hand, Germany showed stable LT annual numbers (from deceased each year) from 2019 to 2021, achieving a remarkable compensation of temporary lower LT rates during both lockdown periods in 2020 [15,16].

Indicative of the problem's severity is the fact that the American Association for the Study of Liver Diseases (AASLD) issued a guideline in July 2020, according to which only liver implants with a low risk of dysfunction could be accepted [17].

The response of LT centers worldwide needs to be studied, aiming to explain the heterogeneity in the recovery of their activity [4]. For example, in Germany, given the

preexisting organ shortage and the additional shrinkage of donor pools during COVID-19 outbreak, a great effort has been made in order to keep the LT activity at the highest possible level [18]. In line to this practice, a recent report from France focuses on the implementation of certain steps aiming to reorganize the LT program. These mainly include resource optimization, improvement of LT candidate risk stratification, optimal organ matching and effective screening protocols for COVID-19 [19].

The aspect of reduced ICU beds was less present in countries with a plethora of available ICU beds or the flexibility to create new ones [5,20]. In countries with shortage of ICU beds (such as Greece), priority was given to COVID-19 cases. The lack of available non-COVID ICU limited the potentiality of LT, when taking into consideration the necessity for intensive postoperative monitoring, as well as the great restriction to the pool of donors [6,21]. It should be noted that patients diagnosed with COVID-19 in need of ICU monitoring were initially considered inappropriate candidates for donation [22,23]. However, there is strong evidence that LT from active COVID-19 donors (low risk donors, with mild infection signs) in selected recipients with COVID-19 immunity could be a safe alternative of expanding organ pool [22,24,25]. The Organ Procurement and Transplantation Network (OPTN) released in April 2022 a guidance based on current evidence and information regarding organ acceptance from donors with a history of COVID-19 [26].

Furthermore, according to the Spanish recommendations, a SARS-CoV-2 PCR positive deceased donor, may be considered as potential "non-standard" risk liver donor, as long as Covid-19 did not represent his cause of death [27].

Moreover, the COVID-19 pandemic has inevitably affected the acceptance of liver allografts and the number of LT in both transplantation centers of our country. LT in our country has become even more burdened, as a consequence of the already small number of solid organ donors in Greece, in combination with the occupancy of ICU beds from COVID-19 patients for the better part of the pandemic and the intrahospital dispersion of the virus. This negative influence, regarding Greece's LT program, is mainly depicted in the second year of pandemic. In more detail, the cumulative annual numbers of performed LTs during 2019 and 2020 were comparable, namely 33 and 32 respectively. A significant decrease to only 24 performed cases has been observed within the year 2021. Fortunately, an increasing tendency was noted during 2022, when 36 LTs were performed, thus providing hope for normalisation (Figure 1).

Notably, many transplantation centers all over the world have implemented practices of virtual appoint-

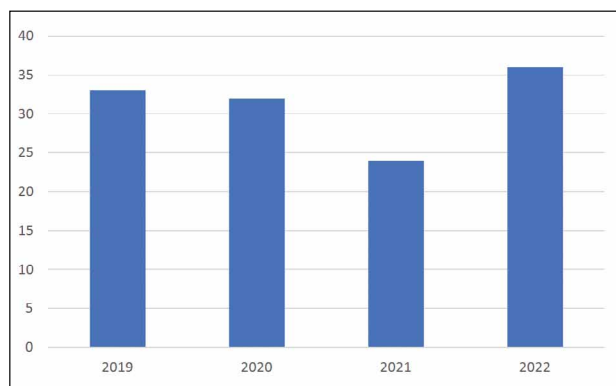


FIGURE 1. Cumulative annual number of liver transplantations performed by the two transplantation centers in Greece from 2019 to 2022. Data provided by the Hellenic Transplant Organization.

ments, enhancement of telemedicine and rolling schedule. Of great concern is the safety not only of the recipient, but of all the involved personnel [28,29]. Healthcare systems characterized by satisfactory organization, competency and ability of adaptation have shown swift recovery in regards to LT through this crisis [11].

Impact of COVID-19 on waiting lists and LT candidates

Furthermore, the pandemic had a negative effect, caused by multiple reasons, on the waiting lists for solid organ transplantation, including the liver. Interestingly, taking into account that many countries restricted their LT activity to urgent cases, all other candidates (including those with liver malignancies) were practically temporarily suspended for LT [30]. Moreover, patients with chronic liver disease or cirrhosis, knowing that they were at increased risk of developing severe clinical form, in case of COVID-19 infection, were afraid of visiting health care units. Consequently, many of them consciously avoided their planned clinic visits [31]. In addition, many candidates decided against undergoing LT during the pandemic due to several reasons. The risk of severe COVID-19 infection course under immunosuppressive therapy, or even the fear of staying alone during the early postoperative course, due to restrictive hospital visitor policies, depict some of them [32]. As a result, an increase in the mortality of patients on waiting lists is being noted [33]. Due to the decreased number of allografts, withdrawal from waiting lists has been noticeably reduced. A reduced number of patients were registered in waiting lists in several countries, an indication of poor follow-up of patients with liver disease [34].

Symptomatic SARS-COV2 infection presented more frequently in LT candidates rather than recipients. One

possible explanation is the fact that recipients are more cautious due to their known immunosuppression [35]. LT candidates suffering from COVID-19 infection, presenting with dyspnea and a MELD score > 15 face are shown to be at an increased risk of early death. Failure of the respiratory system was one of the main reasons to declare candidates ineligible. In order to be reactivated on the waiting lists, the patients have to be asymptomatic, with at least one or two negative SARS-COV2 tests. According to a multicenter cohort study no need for hospitalisation was linked to better survival, while patients with acute-on-chronic liver failure faced higher mortality [36].

Vaccination for preventable diseases is generally recommended early after the underlying disease is diagnosed [37]. Severe COVID-19 can be prevented, so pre-LT vaccination is generally recommended [38]. In cases that this is not a feasible option, the social circle of the candidate should get vaccinated. The first three-six months following LT, vaccination is advised to be avoided, due to decreased response of the immune system [39]. High dispersion of the virus provides reason for early vaccination after the transplant, but no sooner than 4 weeks. Also, acute cellular rejection is a contraindication against vaccination [40].

Impact of COVID-19 on LT recipients

The prevailing symptoms of LT recipients with COVID-19 include fever, cough and dyspnoea. It is interesting to note that abdominal symptoms and especially diarrhea were encountered more frequently in LT recipients rather than the general population. The presentation of diarrhea may be linked to the use of MMF [41].

The majority of liver recipients infected by SARS-COV2 are hospitalised, presenting increased risk of death when admitted to the ICU. Age, kidney function, the presence of history or active cancer and comorbidities seem to play an important role to survival. According to some studies, less symptoms were observed in patients infected early after transplantation [4,42]. Results, recently published, by a high-volume center, indicate that mortality rates in liver recipients infected by SARS-COV2 are higher in elective surgeries when compared to cases of acute liver failure [43].

Complete discontinuation of immunosuppression therapy did not prove to be beneficial. A positive effect on survival was noticed by the use of tacrolimus, possibly by inhibiting the replication of the virus and affecting the immunological response. Calcineurin inhibitors were continued in the majority of patients, but with reduced doses, while MMF was identified as independent predictors of severe disease [41,44,45].

Moreover, some reports of worse outcomes of LT during pandemic, (compared with the pre-COVID period) should

not be overseen [46]. Several factors may have contributed to these unfavorable results. One of the most significant seems to be the fact that many centers limited their LT procedures to only life-threatening situations. The policy of transplanting much sicker patients is unavoidably associated with longer hospital stay and higher complication rates in general. Further negative influencing factors seem to be the lack of blood products, the understaffing and the restriction to logistics related to LT during pandemic.

CONCLUSION

Therefore, it becomes clear that in order to protect the vulnerable field of LT in an era of crisis, optimisation of crisis management practices and reinforcement of the existing units are necessary measures. LT programs can only be conducted in big hospital institutions with long and multidisciplinary experience. During this period, plenty of changes were recognized in the field of LT. Our concern should be the proper treatment of patients, taking into consideration their safety. In order to provide them with the appropriate care more studies need to be conducted, focusing on the right time interval between vaccination or/and infection and liver transplant, as well as the handling of immunosuppression therapy. Furthermore, it is of crucial importance to recognize and study the possible risks and benefits of using grafts from COVID-19 patients with mild or severe disease, in order to once again expand the pool of donors. Overall, the COVID-19 pandemic has had a profound impact on LT worldwide, highlighting the need for continued research and adaptation to ensure that patients with liver disease can receive timely and appropriate care, even in times of crisis.

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REFERENCES

1. Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, et al. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. *BMJ Open* [Internet]. 2021 Mar;11(3):e045343. Available from: <https://pubmed.ncbi.nlm.nih.gov/33727273/>
2. Khan M, Adil SF, Alkhatlan HZ, Tahir MN, Saif S, Khan M, et al. COVID-19: A global challenge with old history, epidemiology and progress so far. *Molecules*. 2020 Dec;26(1):39.
3. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed*. 2020 Mar;91(1):157-60.
4. Russo FP, Izzy M, Rammohan A, Kirchner VA, Di Maira T, Belli LS, et al. Global impact of the first wave of COVID-19 on liver transplant centers: A multi-society survey (EASL-ESOT/ELITA-ILTS). *J Hepatol*. 2022 Feb;76(2):364-70.
5. Zaidan M, Legendre C. Solid organ transplantation in the era of COVID-19: Lessons from France. *Transplantation*. 2021 Jan;105(1):61-66
6. Putzer G, Gasteiger L, Mathis S, van Enckevort A, Hell T, Resch T, et al. Solid organ donation and transplantation activity in the eurotransplant area during the first year of COVID-19. *Transplantation*. 2022 Jul;106(7):1450-4.
7. Lewis A, Koukoura A, Tsianos GI, Gargavanis AA, Nielsen AA, Vassiliadis E. Organ donation in the US and Europe: The supply vs demand imbalance. *Transplant Rev (Orlando)*. 2021 Apr;35(2):100585.
8. Stone KW, Kintziger KW, Jagger MA, Horney JA. Public health workforce burnout in the COVID-19 response in the U.S. *Int J Environ Res Public Health*. 2021 Apr;18(8):4369.
9. Lasater KB, Aiken LH, Sloane DM, French R, Martin B, Reneau K, et al. Chronic hospital nurse understaffing meets COVID-19: an observational study. *BMJ Qual Saf*. 2021;30(8):639-47.
10. Stanworth SJ, New HV, Apolseth TO, Brunskill S, Cardigan R, Doree C, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. *Lancet Haematol*. 2020 Oct;7(10):e756-64.
11. Kute VB, Tullius SG, Rane H, Chauhan S, Mishra V, Meshram HS. Global Impact of the COVID-19 Pandemic on Solid Organ Transplant. *Transplant Proc*. 2022 Jul-Aug;54(6):1412-6.
12. Servin-Rojas M, Olivas-Martinez A, Ramirez Del Val F, Torres-Gomez A, Navarro-Vargas L, Garcia-Juarez I. Transplant trends in Mexico during the COVID-19 pandemic: Disparities within healthcare sectors. *Am J Transplant*. 2021 Dec;21(12):4052-60.
13. Turco C, Lim C, Soubrane O, Malaquin G, Kerbaul F, Bastien O, et al. Impact of the first Covid-19 outbreak on liver transplantation activity in France: A snapshot. *Clin Res Hepatol Gastroenterol*. 2021 Jul;45(4):101560.
14. Global Observatory on Donation and Transplantation (GODT), WHO-ONT collaboration [Internet]. 2021. Available from: <https://www.transplant-observatory.org/who-ont/>
15. Eurotransplant [Internet] 2023. Available from: [statistics.eurotransplant.org](https://www.eurotransplant.org)
16. Yurttas C, Schleicher C, Fischer I, Meisner C, Nadalin S, Konigsrainer A, et al. Impact of the SARS-CoV-2 pandemic on liver surgery and liver transplantations in Germany. *Zentralbl Chir*. 2022 Aug;147(4):354-60.
17. Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. *Hepatology*. 2020 Jul;72(1):287-304.
18. Hugo C, Strassburg C, Stecher M, Rahmel A. Stable and safe organ procurement and transplantation during SARS-CoV-2 pandemic in Germany. *Transpl Int*. 2020 Oct;33(10):1335-6.

19. Muller X, Tilmans G, Chenevas-Paule Q, Lebosse F, Antonini T, Poinot D, et al. Strategies for liver transplantation during the SARS-CoV-2 outbreak: Preliminary experience from a single center in France. *Am J Transplant*. 2020 Nov;20(11):2989-96.
20. Cardoso FS. Liver transplantation in an ICU dominated by COVID-19. *Liver Transpl*. 2020 Aug;26(8):1064-65.
21. Sotiropoulos GC, Machairas N, Kostakis ID, Kouraklis G. The struggle for intensive care coverage after hepatic resections: the Greek reality. *Lancet*. 2017 Jan;389(10067):364-5.
22. Martinez-Reviejo R, Tejada S, Cipriano A, Karakoc HN, Manuel O, Rello J. Solid organ transplantation from donors with recent or current SARS-CoV-2 infection: A systematic review. *Anaesth Crit Care Pain Med*. 2022 Aug;41(4):101098.
23. Jayasekera CR, Vikram HR, Rifat Z, Wagler J, Okubo K, Braaksma BR, et al. Solid Organ Transplantation From SARS-CoV-2-infected Donors to Uninfected Recipients: A Single-center Experience. *Transplant Direct*. 2022 Jan;8(2):e1286.
24. Romagnoli R, Gruttadauria S, Tisone G, Maria Ettorre G, De Carlis L, Martini S, et al. Liver transplantation from active COVID-19 donors: A lifesaving opportunity worth grasping? *Am J Transplant*. 2021 Dec;21(12):3919-25.
25. Wall AE, McKenna GJ, Onaca N, Ruiz R, Bayer J, Fernandez H, et al. Utilization of a SARS-CoV-2-positive donor for liver transplantation. *Proc (Bayl Univ Med Cent)*. 2022;35(1):62-3.
26. Organ Procurement and Transplantation Network (OPTN) [Internet] [Accessed 2022 Sep]. Available from: optn.transplant.hrsa.gov/media/kkhn1wah/sars-cov-2-summary-of-evidence.pdf Accessed September 2022
27. Montiel Villalonga P, Martinez-Alpuente I, Fernandez-Ruiz M, Len O, Bodro M, Los-Arcos I, et al. Transplantation of organs from SARS-CoV-2-positive donors: Preliminary experience from Spain. *Transpl Infect Dis*. 2023 Feb;25(1):e14008.
28. Gonzalez AJ, Kapila N, Thomas E, Pinna A, Tzakis A, Zervos XB. Managing liver transplantation during the COVID-19 pandemic: A survey among transplant centers in the Southeast United States. *World J Hepatol*. 2021 Dec;13(12):2161-7.
29. Kumar D, Manuel O, Natori Y, Egawa H, Grossi P, Han SH, et al. COVID-19: A global transplant perspective on successfully navigating a pandemic. *Am J Transplant*. 2020 Jul;20(7):1773-9.
30. Tzedakis S, Jeddou H, Housset-Debry P, Sulpice L, Boudjema K. COVID-19: Thoughts and comments from a tertiary liver transplant center in France. *Am J Transplant*. 2020 Jul; 20(7): 1952-3.
31. Mendizabal M, Ridruejo E, Pinero F, Anders M, Padilla M, Toro LG, et al. Comparison of different prognostic scores for patients with cirrhosis hospitalized with SARS-CoV-2 infection. *Ann Hepatol*. 2021 Nov-Dec;25:100350.
32. 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 Feb;395(10223):497-506.
33. Yuan Q, Haque O, Coe TM, Markmann JF. The Heterogeneous Effect of COVID-19 on Liver Transplantation Activity and Waitlist Mortality in the United States. *Front Surg*. 2021 May;18:8:669129. Available from: <https://pubmed.ncbi.nlm.nih.gov/34095209/>
34. Miller J, Wey A, Valapour M, Hart A, Musgrove D, Hirose R, et al. Impact of COVID-19 pandemic on the size of US transplant waiting lists. *Clin Transplant*. 2022 May;36(5):e14596.
35. Polak WG, Fondevila C, Karam V, Adam R, Baumann U, Germani G, et al. Impact of COVID-19 on liver transplantation in Europe: alert from an early survey of European Liver and Intestine Transplantation Association and European Liver Transplant Registry. *Transpl Int*. 2020 Oct;33(10):1244-52.
36. Belli LS, Duvoux C, Cortesi PA, Facchetti R, Iacob S, Pericone G, et al. COVID-19 in liver transplant candidates: pretransplant and post-transplant outcomes - an ELITA/ELTR multicentre cohort study. *Gut*. 2021 Oct;70(10):1914-24.
37. Stucchi RSB, Lopes MH, Kumar D, Manuel O. Vaccine Recommendations for Solid-Organ Transplant Recipients and Donors. *Transplantation*. 2018 Feb;102(2S Suppl 2):S72-S80.
38. Sripongpun P, Pinpathomrat N, Bruminhent J, Kaewdech A. Coronavirus Disease 2019 Vaccinations in Patients With Chronic Liver Disease and Liver Transplant Recipients: An Update. *Front Med (Lausanne)*. 2022 Jun;9:924454.
39. Cornberg M, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. *J Hepatol*. 2021 Apr;74(4):944-51.
40. Rolak S, Said A, German R, Hayney MS, Caldera F. Optimizing Immunization Strategies in Adult Patients With Chronic Liver Disease and Liver Transplant Recipients. *Gastroenterol Hepatol (N Y)*. 2022 Apr;18(4):196-206.
41. Belli LS, Fondevila C, Cortesi PA, Conti S, Karam V, Adam R, et al. Protective Role of Tacrolimus, Deleterious Role of Age and Comorbidities in Liver Transplant Recipients With Covid-19: Results From the ELITA/ELTR Multi-center European Study. *Gastroenterology*. 2021 Mar;160(4):1151-63.e3.
42. Webb GJ, Marjot T, Cook JA, Aloman C, Armstrong MJ, Brenner EJ, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. *Lancet Gastroenterol Hepatol*. 2020 Nov;5(11):1008-16.
43. Moradi A, Hadizadeh A, Ghiasvand F, Ahmadinejad Z, Toosi MN, Ghazi S, et al. Does COVID-19 infection significantly affect liver transplantation? Results of liver transplantation in the COVID-19 era at a single, high-volume centre. *BMJ Open Gastroenterol [Internet]*. 2023 Feb;10(1):e001084. Available from: <https://pubmed.ncbi.nlm.nih.gov/36746522/>
44. Jayant K, Reccia I, Viridis F, Pyda JS, Bachul PJ, di Sabato D, et al. COVID-19 in hospitalized liver transplant recipients: An early systematic review and meta-analysis. *Clin Transplant*. 2021 Apr;35(4):e14246.
45. Colmenero J, Rodriguez-Peralvarez M, Salcedo M, Arias-Milla A, Munoz-Serrano A, Graus J, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol*. 2021 Jan;74(1):148-55.
46. Mendizabal M, Pages J, Pinero F, Thompson M, Silva MO. Liver transplant outcomes during the COVID-19 pandemic. *Ann Hepatol*. 2022 Mar-Apr;27(2):100656.