Living Donner Liver Transplant in Hepatocellular Carcinoma

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Abstract:

Liver transplantation for hepatocellular carcinoma (HCC) is the best treatment option for patients with early-stage tumours and accounts for ∼20–40% of all liver transplantations performed at most centres worldwide. The Milan criteria are the most common criteria to select patients with HCC for transplantation but they can be seen as too restrictive. Several proposals have been made for a moderate expansion of the criteria, which result in good outcomes but with an increase in the risk of tumour recurrence. Novel surgical techniques have been developed to increase the available pool of organs for liver transplantation (such as living donor liver transplantation, donation after circulatory death and split livers), but the effect of these techniques on patients with HCC is still under debate.

Keywords: Liver Transplantation, Hepatocellular Carcinoma, Milan Criteria.

Introduction:

From an oncologic perspective, liver transplantation is theoretically the optimal treatment option, since total hepatectomy eliminates unrecognized intrahepatic metastasis as well as the possibility of de novo HCC arising from the underlying liver disease, and it removes cirrhotic liver tissue **(1).**

In March 1st 1963, Starzl et al. did the first liver transplantation in the world. The patient was an 3-year-old boy with biliary atresia who underwent liver transplantation, however, he died during the surgery because of coagulation disorder and uncontrolled bleeding**(2).**

In July 1989, Strong *et al.* performed the first successful transplantation of a liver graft from a living related donor; the donor was a 29-year-old woman and the recipient was her 17-month-old son **(3).** The first adult LDLT was performed in 1994**(4).**

When orthotopic liver transplantation (OLT) was first introduced, it was offered to patients with unresectable disease secondary to tumor burden or liver dysfunction, and in so doing, the survival rates were low and recurrence rates were high **(5).** the Milan criteria were established In an attempt to improve survival following OLT, a clear cut patient selection criteria according to tumor number and size had been adopted by most transplant centers and the long-term survival of over 80% was consistently achieved **(6).**

In Egypt, a deceased donor liver transplantation (DDLT) program is still awaited, thus, LDLT is the only hope for patients with end-stage liver disease or HCC in the presence of cirrhosis **(7).**

Living donor liver transplant (LDLT) was first performed in Egypt in 1991 by the surgical team at the National Liver Institute (NLI), Menoufeya University, with the help of Prof. Habib and recipient survival was 11 months **(8).**

The regulations were made by the Egyptian medical syndicate. Programs started with the assistance and under supervision of oversea teams. The breakthrough was made in Dar Al-Fouad Hospital by starting the program of LDLT (August 2001), with Prof. Tanaka, Kyoto University, Japan. This was followed by Wady El-Neel Hospital (October 2001), NLI, Menoufeya University (April 2003) and Maadi Armed Forces Hospital (September 2003) **(9).**

In Egypt between July 2018 and January 2020, 380 LDLT operations were performed **(10).**

Nowadays, HCC patients have the highest rates of waitlisting for liver transplantation among all candidates with end-stage liver disease, shortage of donor organs has resulted in an overall increase of waiting time with an increased risk of waitlist dropout due to tumor progression in HCC patients **(11).**

Egyptian study for HCC LDLT between August 2001 and June 2012 show 1-, 3-, and 5-year survival rates were 98.3%, 93.5%, and 71.4% overall survival **(12).**

A multidisciplinary approach including a medical oncologist, transplant hepatologist, transplant surgeon, surgical oncologist, radiation oncologist, interventional radiologist, and radiologist should be utilized for all patient management plans **(13).**

Selection Criteria for Liver Transplantation

For more than 25 years, Milan criteria (1 nodule ≤ 5 cm or 3 nodules ≤ 3 cm with no macrovascular invasion on pre-LT imaging) have been considered as the benchmark for LT because 5-year survival rate > 70% **(14).**

Milan criteria for liver transplantation as a treatment option for HCC (15).

Expanded criteria

• **UCSF:** Single lesion ≤6.5 cm or ≤3 lesions with the largest being ≤4.5 cm and a total diameter ≤8 cm **(16).**

• **Up-to-7:** 7 cm as the sum of the size of the largest tumor and the number of tumors. No vascular Invasion **(17).**

• **Toronto criteria:** Any tumor size or number. All lesions require a liver biopsy and must not show poor differentiation. No extra-hepatic metastasis, venous/biliary thrombosis OR cancer related symptoms **(18).**

UNOS Criteria for Downstaging (19).

• Single lesion >5 cm but ≤8 cm

• 2-3 lesions each ≤5 cm with total diameter of all lesions ≤8cm

• 4-5 lesions each ≤3 cm with total diameter of all lesions ≤8 cm

The Milan criteria remain the most frequently applied criteria for liver allocation, with 97% of all transplanted livers from 2002 to 2007 meeting Milan criteria, while only 3% fit UCSF criteria **(20).**

Over time, the focus has shifted to incorporate markers of tumor biology into LT selection guidelines that have traditionally been based only on tumor size and number, studies have demonstrated that combining alpha-fetoprotein (AFP) with tumor burden discriminates prognosis after LT better than using tumor burden alone **(21).**

Contraindications for

Patients with a low MELD score, advanced cardiac or pulmonary disease, active sepsis, grave psychological disorder, or active alcohol or drug abuse are absolutely ineligible for liver transplantation **(22).**

HCC or perihilar cholangiocarcinoma with metastatic spread are absolute contraindications for transplant **(23).** recent developments have allowed some centers to perform liver transplantation for patients with under HIV treatment **(24).** AFP >1,000 ng/ml should be considered an absolute contraindication to liver transplantation regardless of tumor burden

Table (1): Characteristics and results of the different allocation systems adopted for liver transplantation in hepatocellular carcinoma **(25).**

Selection system	Year of proposal	Criteria	Survival/years of follow-up
Milan criteria	1996	Single lesion ≤ 5 cm; up to three separate lesions, none larger than 3 cm; no evidence of gross vascular invasion; and no regional nodal or distant metastases	85%/4
University of California, San Francisco criteria	2007	Single nodule up to 6.5 cm or up to three lesions, the largest of which is 4.5 cm or smaller and the sum of the diameters no larger than 8 cm	80.9%/5
Up-to-seven criteria	2009	Sum of size (in cm) of larger tumor plus number of tumors ≤ 7	71.2%/5
Total tumor volume and AFP Criteria	2009	Total tumor volume ≤ 115 cm3 and AFP ≤ 400 ng/mL, without macrovascular invasion or extrahepatic disease	74.6%/4
Kyoto criteria	2013	≤ 10 tumors; ≤ 5 cm; and des gammacarboxy prothrobine ≤ 400 mAU/mL	65%/5
Extended Toronto criteria	2016	Any size or number of tumors, without systemic cancer-related symptoms, extrahepatic disease, vascular invasion, or a poorly differentiated largest lesion at percutaneous tumor biopsy	68%/5
5-5-500 rule Multi-center, Japan	2019	Tumor size ≤ 5 cm in diameter Tumor number ≤ 5 AFP value ≤ 500 ng/ml	75.8% /5

Post transplant immunosuppressive regimens:

In all HCC patients (regardless of their risk of relapse), strategies to facilitate CNI reduction should be implemented to limit CNI-related renal toxicities and the impact of CNI exposure on cancer recurrence **(26).**

Clinical evidence has shown that mTOR inhibitors can limit HCC recurrence and progression in liver transplant recipients**(27).** mTOR inhibitors were also associated with significantly lower rates of HCC recurrence after liver transplantation when compared with CNIs **(28).**

HCC recurrence is one of the most threatening complications after LT with recurrence rates of approximately 17% **(29).**

The recurrence of HCC can be located in the liver or extrahepatic, and it is important to differentiate between recurrent HCC and other lesions using arterial phase enhancement. Early detection of HCC recurrence after LT is crucial for optimal management **(30).**

Initially some studies showed higher recurrence in patients transplanted with living donor and investigators hypothesized that rapid regeneration process of partial liver graft and cytokine released might induce the early recurrence of potential microscopic HCC. Another explanation was that the fast-track feature of LDLT and short observation period before liver transplantation may mask the aggressiveness of HCC which leads to higher recurrence **(31).**

However, more recent meta-analyses revealed equal or even better outcomes of LDLT than DDLT in both patient survival and disease-free survival, and now it has become consensus that patients with HCC meeting the indication criteria and beyond the indication for locoregional treatments will be benefitted by LDLT if they have appropriate live donors **(32).**

Predictors of HCC recurrence include: patient related factors (underlying disease and hepatitis C virus treatment), the tumor related factors (tumor staging, vascular invasion, and differentiation grade), biomarkers (alpha-fetoprotein and the neutrophil lymphocyte ratio), radiological factors and treatment related factors (time on the waiting list, pre-transplant bridging therapy, and response to locoregional treatment (LRT))**(33).**

The best characterized postoperative prediction model is the Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score which is based on the sum of the largest viable tumor diameter and number of viable tumors on explant, the presence of microvascular invasion, and the alpha-fetoprotein (AFP) level at the time of LT **(34).**

Considered the known risk of recurrence of HCC after LT, patients deserve periodical monitoring for cancer reappearance. Surveillance exerts its benefit on prognosis through the identification of early recurrence, allowing in turn the applicability of potentially curative treatments **(35).**

surveillance after LT should be tailored according to the known pattern of recurrence Timing of HCC recurrence is variable, but in the majority of cases it occurs 2–3 years after LT Early recurrence (defined as <1 year after LT) is associated with a significantly worse prognosis **(36).**

The treatment of recurrence after LT can result in prolonged survival but its strategies remain a challenge with the fact of high incidence of extrahepatic recurrence **(37).** patients treated with Sorafenib (SOR) and everolimus (EVL)might have synergetic effect for improve patients survival after recurrence **(38).**

MELD score is used to assess disease severity for the purpose of defining a patient's listing status for LT, higher MELD scores reflect more severe disease, poorer prognosis and greater likelihood of LT, barring any absolute contraindications to transplantation **(39).** One of the HCC staging systems, Model to Estimate Survival In Ambulatory HCC (MESIAH), includes the MELD score as one of its components **(40).**

In 2016, the MELD score was updated to include serum sodium, an objective biomarker that is often a surrogate indicator for ascites. A new update to and recalibration of the MELD score, MELD 3.0, was recently published with the inclusion of sex and serum albumin **(41).**

While patients with HCC may be granted exception points that are added to their scores, the MELD system was not designed to assess HCC disease severity, and it does not provide good prognostic classification for these patients**(42).**

The MELD exception points for patients with HCC, decreases wait-list mortality and increases priority for LT. By for the commonest indication of MELD exception point is HCC in united states**(43).**

The 1st HCC exception points policy was implemented on February 27, 2002. Since then, significantly high number of patients with HCC have been transplanted. Secondary to donor organ shortage and high number of patients being transplanted for HCC, needing multiple revisions of UNOS MELD-exception allocation policy for HCC over the last 2 decades **(44).**

MELD equivalent that matches HCC patients to non-HCC patients by the same numerical MELD score and developed the equation: HCC-MELD (1.27∗MELD - 0.51∗logAFP+4.59), whereby the same transplant benefit between the two groups was achieved **(45).**

The current organ allocation policy mandates to list the patient with actual Na-MELD of the patient and after 3 mo, request a MELD extension. Once 6 mo' observation period is finished and the patient is still in with in MILAN criteria, the patient will be granted HCC-MELD exception points. The maximum points are median MELD at transplant (MMaT) 2. The MMaT remains fixed score and does not increase every 3 mo. By using previous 12 mo' data, the median MELD is recalculated every 6 mo and subsequently MMaT is readjusted. The purpose of this change was to promote more balanced allocation of donor organs between HCC and non-HCC patients on liver

transplant wait list. 6 mo wait list observation period for HCC patients also will provide better understanding to assess the tumor biology**(46).**

Wait listed patient within MILAN criteria (T2 lesion) and AFP ≤ 1000 ng/mL will be eligible for standardized MELD exception points. If AFP > 1000 ng/mL with T2 lesion, candidates may be treated with local-regional therapy (LRT): (1) After treatment if AFP < 500 ng/mL, eligible for standardized MELD exception points; and (2) After treatment if AFP > 500 ng/mL, candidate would need to be referred to and NLRB for MELD exception points**(47).**

Salvage liver transplantation:

Salvage LT has been espoused as a strategy for patients with HCC who have undergone resection and develop either liver decompensation or tumor recurrence within acceptable LT criteria **(48).**

References:

1. **E. De Martin, T. Berg, D. Samuel, M. Berenguer, P. Burra, C. Fondevila, J. K. Heimbach, G.-P. Pageaux, A. Sanchez-Fueyo and C. Toso(2024):**EASL Clinical Practice Guidelines on liver transplantation.Journal of Hepatology,81(6),1040-1086.
2. **T. E. STARZL, T. Marchioro, K. Von Kaulla, G. Hermann, R. Brittain and W. Waddell(1963):**Homotransplantation of the liver in humans.Surgery, gynecology & obstetrics,117(659.
3. **R. W. Strong, S. V. Lynch, T. H. Ong, H. Matsunami, Y. Koido and G. A. Balderson(1990):**Successful liver transplantation from a living donor to her son.New England Journal of Medicine,322(21),1505-1507.
4. **S. Lee, K. Park, S. Hwang, Y. Lee, K. Kim, C. Ahn, D. Choi, S. Joo, J. Jeon and C. Chu(2002):**Adult-to-adult living donor liver transplantation at the Asan Medical Center, Korea.Asian journal of surgery,25(4),277-284.
5. **H. Bismuth, L. Chiche, R. Adam, D. Castaing, T. Diamond and A. Dennison(1993):**Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients.Annals of surgery,218(2),145.
6. **V. Mazzaferro, E. Regalia, R. Doci, S. Andreola, A. Pulvirenti, F. Bozzetti, F. Montalto, M. Ammatuna, A. Morabito and L. Gennari(1996):**Liver transplantation

for the treatment of small hepatocellular carcinomas in patients with cirrhosis.New England Journal of Medicine,334(11),693-700.

7. **M. A. Wahab, H. Hamed, T. Salah, W. Elsarraf, M. Elshobary, A. M. Sultan, A. Shehta, O. Fathy, H. Ezzat and A. Yassen(2014):**Problem of living liver donation in the absence of deceased liver transplantation program: Mansoura experience.World Journal of Gastroenterology: WJG,20(37),13607.

8. **N. Habib, B. Higgs, I. Marwan, R. El-Masry, A. Helmi, R. Saifi, A. Abbas, F. Abdel-Wohab, A. Abaza and H. Koensa(1993):**Living-related liver transplantation in Africa.International surgery,78(2),121-123.

9. **K. E. Amer and I. Marwan(2016):**Living donor liver transplantation in Egypt.Hepatobiliary surgery and nutrition,5(2),98.

10. **Abd Elbaset, H. S., Sultan, A. M., Montasser, I. F., Soliman, H. E., Elayashy, M., Makhlouf, N. A., & Scientific Committee of Ministry of Health (MOH) National Project of Waiting Lists, Egypt. (2021).** Egyptian protocol for living donor liver transplantation (LDLT) during SARS-CoV-2 pandemic.

11. **Y.-I. Yoon, K.-H. Kim, S. Hwang, C.-S. Ahn, D.-B. Moon, T.-Y. Ha, G.-W. Song and S.-G. Lee(2024):**Outcomes of 6000 living donor liver transplantation procedures: a pioneering experience at ASAN Medical Center.Updates in Surgery,1-9.

12. **R. Kamel, Y. Hatata, K. Hosny, A. Nabil, A. Mostafa, A. Abdel-Aal, M. Elganzoury, O. Elmalt, I. Marwan and A. Hosny(2017):**Outcome of Living-Donor Liver Transplant for Hepatocellular Carcinoma: 15-Year Single-Center Experience in Egypt.Experimental and Clinical Transplantation: Official Journal of the Middle East Society for Organ Transplantation,15(Suppl 2),12-20.

13. **A. C. Yopp, J. C. Mansour, M. S. Beg, J. Arenas, C. Trimmer, M. Reddick, I. Pedrosa, G. Khatri, T. Yakoo and J. J. Meyer(2014):**Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome.Annals of surgical oncology,21(4),1287-1295.

14. **P.-A. Clavien, M. Lesurtel, P. M. Bossuyt, G. J. Gores, B. Langer and A. Perrier(2012):**Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report.The lancet oncology,13(1),e11-e22.

15. **W. Abdelhamed and M. El-Kassas(2023):**Hepatocellular carcinoma recurrence: Predictors and management☆.Liver Research,

16. **F. Yao, L. Xiao, N. Bass, R. Kerlan, N. Ascher and J. Roberts(2007):**Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging.American Journal of Transplantation,7(11),2587-2596.

17. **V. Mazzaferro, J. M. Llovet, R. Miceli, S. Bhoori, M. Schiavo, L. Mariani, T. Camerini, S. Roayaie, M. E. Schwartz and G. L. Grazi(2009):**Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis.The lancet oncology,10(1),35-43.

18. **G. Sapisochin, N. Goldaracena, J. M. Laurence, M. Dib, A. Barbas, A. Ghanekar, S. P. Cleary, L. Lilly, M. S. Cattral and M. Marquez(2016):**The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study.Hepatology,64(6),2077-2088.

19. **F. Y. Yao, N. Mehta, J. Flemming, J. Dodge, B. Hameed, O. Fix, R. Hirose, N. Fidelman, R. K. Kerlan Jr and J. P. Roberts(2015):**Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria.Hepatology,61(6),1968-1977.

20. **S. S. Patel, A. K. Arrington, S. McKenzie, B. Mailey, M. Ding, W. Lee, A. Artinyan, N. Nissen, S. D. Colquhoun and J. Kim(2012):**Milan criteria and UCSF criteria: a preliminary comparative study of liver transplantation outcomes in the United States.International journal of hepatology,2012(

21. **V. Mazzaferro, C. Sposito, J. Zhou, A. D. Pinna, L. De Carlis, J. Fan, M. Cescon, S. Di Sandro, H. Yi-Feng and A. Lauterio(2018):**Metroticket 2.0 model for analysis

of competing risks of death after liver transplantation for hepatocellular carcinoma.Gastroenterology,154(1),128-139.

22. **V. Mazzaferro, Chun, Y. S., Poon, R. T., Schwartz, M. E., Yao, F. Y., Marsh, J. W., ... & Lee, S. G. (2008).** Liver transplantation for hepatocellular carcinoma. Annals of surgical oncology, 15, 1001-1007.
23. **G. G. Panayotova, F. Paterno, J. V. Guarrera and K. E. Lunsford(2020):**Liver transplantation for cholangiocarcinoma: insights into the prognosis and the evolving indications.Current Oncology Reports,22(1-11.
24. **N. A. Terrault, C. Francoz, M. Berenguer, M. Charlton and J. Heimbach(2023):**Liver Transplantation 2023: Status Report, Current and Future Challenges.Clinical Gastroenterology and Hepatology,
25. **F. Santopaolo, I. Lenci, M. Milana, T. M. Manzia and L. Baiocchi(2019):**Liver transplantation for hepatocellular carcinoma: Where do we stand?World journal of gastroenterology,25(21),2591.
26. **U. Cillo, L. De Carlis, M. Del Gaudio, P. De Simone, S. Fagiuoli, F. Lupo, G. Tisone and R. Volpes(2020):**Immunosuppressive regimens for adult liver transplant recipients in real-life practice: consensus recommendations from an Italian Working Group.Hepatology International,14(930-943.
27. **C. Toso, S. Merani, D. L. Bigam, A. J. Shapiro and N. M. Kneteman(2010):**Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma.Hepatology,51(4),1237-1243.
28. **A. A. Schnitzbauer, N. Filmann, R. Adam, P. Bachellier, W. O. Bechstein, T. Becker, S. Bhoori, I. Bilbao, J. Brockmann and P. Burra(2020):**mTOR inhibition is most beneficial after liver transplantation for hepatocellular carcinoma in patients with active tumors.Annals of surgery,272(5),855-862.

29. **N. El-Domiaty, F. Saliba, E. Vibert, V. Karam, R. Sobesky, W. Ibrahim, G. Pittau, O. Ciacio, C. Salloum and K. Amer(2021):**Early Versus Late Hepatocellular Carcinoma Recurrence After Transplantation: Predictive Factors, Patterns, and Long-term Outcome.Transplantation,105(8),1778-1790.

30. **T. A. Addissouky, I. E. T. E. Sayed, M. M. Ali, Y. Wang, A. E. Baz, A. A. Khalil and N. Elarabany(2024):**Latest advances in hepatocellular carcinoma management and prevention through advanced technologies.Egyptian Liver Journal,14(1),2.

31. **B. Zhu, J. Wang, H. Li, X. Chen and Y. Zeng(2019):**Living or deceased organ donors in liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis.Hpb,21(2),133-147.

32. **B. E. Elkomos, M. Abdo, R. Mamdouh and A. Abdelaal(2023):**Can living donor liver transplantation provide similar outcomes to deceased-donor liver transplantation for hepatocellular carcinoma? A systematic review and meta-analysis.Hepatology International,17(1),18-37.

33. **N. A. Filgueira(2019):**Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation.World journal of hepatology,11(3),261.

34. **A. A. M. Al-Ameri, X. Wei, X. Wen, Q. Wei, H. Guo, S. Zheng and X. Xu(2020):**Systematic review: risk prediction models for recurrence of hepatocellular carcinoma after liver transplantation.Transplant International,33(7),697-712.

35. **G. Sapisochin, N. Goldaracena, S. Astete, J. Laurence, D. Davidson, E. Rafael, L. Castells, C. Sandroussi, I. Bilbao and C. Dopazo(2015):**Benefit of treating hepatocellular carcinoma recurrence after liver transplantation and analysis of prognostic factors for survival in a large Euro-American series.Annals of surgical oncology,22(2286-2294.

36. **T. Hibi, O. Itano, M. Shinoda and Y. Kitagawa(2017):**Liver transplantation for hepatobiliary malignancies: a new era of “Transplant Oncology” has begun.Surgery today,47(403-415.

37. **R. Nevola, R. Ruocco, L. Criscuolo, A. Villani, M. Alfano, D. Beccia, S. Imbriani, E. Claar, D. Cozzolino and F. C. Sasso(2023):**Predictors of early and late hepatocellular carcinoma recurrence.World journal of gastroenterology,29(8),1243.

38. **H. Nitta, A. Younes, N. El-domiaty, V. Karam, R. Sobesky, E. Vibert, A. Coilly, T. Maria Antonini, E. De Martin and D. Cherqui(2021):**High trough levels of everolimus combined to sorafenib improve patients survival after hepatocellular carcinoma recurrence in liver transplant recipients.Transplant International,34(7),1293-1305.

39. **N. Kemmer, V. Zacharias, T. E. Kaiser and G. W. Neff(2009):**Access to liver transplantation in the MELD era: role of ethnicity and insurance.Digestive diseases and sciences,54(8),1794-1797.

40. **J. D. Yang, W. R. Kim, K. W. Park, R. Chaiteerakij, B. Kim, S. O. Sanderson, J. J. Larson, R. A. Pedersen, T. M. Therneau and G. J. Gores(2012):**Model to estimate survival in ambulatory patients with hepatocellular carcinoma.Hepatology,56(2),614-621.

41. **W. R. Kim, A. Mannalithara, J. K. Heimbach, P. S. Kamath, S. K. Asrani, S. W. Biggins, N. L. Wood, S. E. Gentry and A. J. Kwong(2021):**MELD 3.0: the model for end-stage liver disease updated for the modern era.Gastroenterology,161(6),1887-1895. e4.

42. **N. A. Wahid, R. Rosenblatt and R. S. Brown Jr(2021):**A review of the current state of liver transplantation disparities.Liver Transplantation,27(3),434-443.

43. **N. D. Parikh and A. G. Singal(2016):**Model for end-stage liver disease exception points for treatment-responsive hepatocellular carcinoma.Clinical Liver Disease,7(5),97.

44. **S. K. Asrani and P. S. Kamath(2015):**Model for end-stage liver disease score and MELD exceptions: 15 years later.Hepatology international,9(3),346-354.

45. **A. Vitale, M. L. Volk, T. M. De Feo, P. Burra, A. C. Frigo, R. R. Morales, L. De Carlis, L. Belli, M. Colledan and S. Fagiuoli(2014):**A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list.Journal of Hepatology,60(2),290-297.

46. **N. L. Latt, M. Niazi and N. T. Pyrsopoulos(2022):**Liver transplant allocation policies and outcomes in United States: a comprehensive review.World Journal of Methodology,12(1),32.

47. **S. Nagai, T. Kitajima, S. Yeddula, R. Salgia, R. Schilke, M. S. Abouljoud and D. Moonka(2020):**Effect of mandatory 6-month waiting period on waitlist and transplant outcomes in patients with hepatocellular carcinoma.Hepatology,72(6),2051-2062.

48. **G. P. Guerrini, G. E. Gerunda, R. Montalti, R. Ballarin, N. Cautero, N. De Ruvo, M. Spaggiari and F. Di Benedetto(2014):**Results of salvage liver transplantation.Liver international,34(6),e96-e104.