Title: Early outcome of machine perfusion vs static cold storage of liver graft: A systemic review and meta-analysis of randomized controlled trials

Running title: Outcome of machine perfusion vs static cold storage of liver graft

[1]Ibrahim Umar Garzali, 0000-0002-9797-851X

[2]Ali Aloun, 0000-0002-6111-5077

[3]Ez el din Abuzeid, 0000-0002-0805-0411

[1]Abdulrahman Abba Sheshe, 0000-0001-5639-2582

[1]Department of Surgery, Aminu Kano Teaching Hospital, Nigeria

[2] Department of Surgery, King Hussein Medical Centre, Jordan

[3] Department of Surgery, Soroka Medical Centre, Israel

Corresponding author:

Dr Ibrahim Umar Garzali

Department of surgery, Aminu Kano Teaching Hospital, Nigeria.

gazaliumar270@yahoo.co.uk

Early outcomes of machine perfusion vs static cold storage of liver graft: A systemic review and meta-analysis of randomized controlled trials

Background and aim: The use of marginal grafts is very challenging and it is associated with post reperfusion syndrome and early allograft dysfunction. The outcomes of machine perfusion for preservation of marginal graft has been compared with that of static cold storage with studies reporting reduced risk of ischemic cholangiopathy and graft loss. We perform this systematic review and meta-analysis of randomized controlled trials (RCTs) comparing outcomes of machine perfusion of liver graft compared to static cold storage (SCS) of liver graft during liver transplantation.

Materials and methods: Two independent researchers thoroughly searched for literature in the following databases: PubMed (Medline), Cochrane Central Register of Controlled Studies (CENTRAL), clinical trial registry, research gate, google scholar and Scopus (ELSEVIER) databases (last search: November 2023). The search terms used were: “dynamic perfusion”, “normothermic perfusion”, “hypothermic perfusion”, “liver transplantation”, “static cold storage”, “NMP”, “HOPE”, “extended criteria grafts”, “Marginal grafts”, “RCTs”, “Randomized controlled trials”, “warm ischemia” and “cold ischemia”.

Results: Eight RCTs published between 2019 to 2023 were included in the data synthesis and meta-analysis. The primary outcome we considered was overall incidence of early allograft dysfunction (EAD) between the two methods of graft perfusion after liver transplantation. The secondary outcome considered was rate of retransplantation. Our meta-analysis revealed that SCS is associated with more EAD when compared with machine perfusion with a P value of <0.00001. We also found that the rate of retransplantation is higher among patients that received liver that was preserved by SCS with a P value of 0.02.

Conclusion: The use of machine perfusion in preservation of liver graft showed significant reduction in early allograft dysfunction and retransplantation.

Keywords: Static cold storage, machine perfusion, liver transplantation, early allograft dysfunction.

Introduction

Since liver transplantation became acceptable therapeutic option for some selected liver diseases, there was marked increased in the demand for liver graft which resulted in lack of adequate ideal grafts for liver transplantation. In an effort to expand the donor pool, transplant

surgeons have increasingly used extended criteria grafts, domino liver grafts and living donor grafts.[1–3]

The use of extended criteria grafts is very challenging and it is associated with more complications such as post reperfusion syndrome, early allograft dysfunction (EAD), primary non function (PNF), vascular and biliary complications among others. These complications may be associated with graft loss or even mortality of patients.[4–7]

One of the risk factors for post-transplant liver dysfunction is ischemic reperfusion injury. Liver transplantation is associated with two forms of liver ischemia both inducing hepatocellular injury.[8–10] The first is cold ischemia which occurs during retrieval of the graft, when the liver is cooled, perfused and then stored in a cold preservation solution (static cold storage {SCS}). The second form of ischemia is the warm ischemia. This is the ischemia encountered during implantation, from removal of the organ from ice until reperfusion or the the ischemia encountered during organ retrieval, from the time of cross clamping (or of asystole in non-heart-beating donors), until cold perfusion is commenced.[11]. The graft is metabolically inhibited during warm and cold ischemia and it becomes more dysfunctional by reperfusion injury after revascularization and reoxygenation.[12,13] An ideal graft can tolerate a long period of cold ischemic time with minimal permanent sequelae. However, extended criteria grafts cannot tolerate prolonged periods of ischemia.[14] To reduce or eliminate this ischemic periods especially in extended criteria grafts, dynamic preservation techniques using ex situ liver perfusion have been utilized.[15–17] There are two main types of ex situ liver perfusion that are clinically available. The first method is the hypothermic oxygenated perfusion (HOPE) which utilizes highly oxygenated (pO2: >60 kPa) artificial solution at hypothermic temperatures (8-12^{0}C). This method is routinely performed after transport of the graft to the recipient center so it

is considered end ischemic. The second method of ex situ perfusion is normothermic machine perfusion (NMP) which aims for a "near-physiological" environment. It utilizes a blood based perfusate to perfuse the graft at 37^0C.[15–17]

The outcomes of dynamic perfusion has been compared with that of static cold storage with initial studies reporting reduced risk of ischemic cholangiopathy and graft loss in patients that received machine perfusion when compared to static cold storage.[18] We perform this systematic review and meta-analysis of randomized controlled trials comparing outcome of machine perfusion of liver graft compared to SCS of liver graft during liver transplantation.

Methods

This systematic review was performed in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline. We prospectively register the protocol for this systematic review in the International Prospective Register of Systematic Reviews, PROSPERO (CRD42023481913).

Search strategy

Two independent researchers thoroughly searched for literature in the following databases: PubMed (Medline), Cochrane Central Register of Controlled Studies (CENTRAL), clinical trial registry, research gate, google scholar and Scopus (ELSEVIER) databases (last search: November 2023). The search terms used were: "dynamic perfusion", "normothermic perfusion", "hypothermic perfusion", "liver transplantation", "static cold storage", "NMP", "HOPE", "extended criteria grafts", "Marginal grafts", "RCTs", "Randomized controlled trials", "warm ischemia" and "cold ischemia". The terms were combined using Boolean logic. Related articles

and reference list were searched to completeness of the search. Conflict was resolved by involving third researcher.

Eligibility criteria

The inclusion criteria for a study to be included for the review are as follow: 1.Studies published from 1990 to date 2.Randomized controlled trials that compared outcomes of liver transplantation in patients whose graft was preserved using SCS and those whose grafts were preserved using machine perfusion. 3. Studies with full texts.

Exclusion criteria are as follows: 1.Conference presentations, editorials and commentaries. 2. Studies in which the relevant data are absent 3.Studies with total sample size of less than 10.

Quality assessment and risk of bias assessment

Jadad score which was developed by Jadad et al[19] was used to assess the quality and bias of the included RCTs. The score ranges from 0-5. A score of 3 and above was considered a good quality study.

Publication bias

If 10 or more studies were included in the meta-analysis of a particular outcome, then publication bias was evaluated using the funnel plot.

Data extraction

Data extraction was performed by 2 independent researchers. The following information was extracted from each study: first author, year of manuscript publication, study design, number of patients in each group, gender of patients per group, mean age of patients in each group, type of

organ preservation technique and outcome data. In case of conflicts between the two researchers, a third researcher is involved to resolve the conflict.

Outcome

The primary outcome of interest is the incidence of PNF per group. The secondary outcome of interest includes incidence of EAD per group. Other outcomes of interest include post reperfusion syndrome, incidence of retransplantation, vascular complication, biliary complication, ICU stay, mortality and graft survival at I year.

Statistical analysis

Statistical analyses were done using RevMan software (version 5.4.1). If the variable is dichotomous, the pooled risk ratio (RR) was calculated with 95 per cent confidence interval. However, if the variable is continuous, the weighted mean difference (WMD) or standardized mean difference (SMD) with 95 per cent CI was calculated from the mean and standard deviation reported from individual studies. If a study did not report the mean and standard deviation, the Wan et al[20] method of extracting mean and standard deviation form median and interquartile range was utilized. Fixed-effects model was used to calculate the pooled effect sizes if the data were not significantly heterogeneous. Otherwise, a random-effects model was used. Heterogeneity was assessed using the I^2 statistics. $I^2 > 50\%$ was considered as a statistically significant heterogeneity. Sensitivity analysis was done by sequential elimination of each of the included studies in the meta-analysis to identify the main source of heterogeneity. Publication bias was evaluated using the funnel plot and Egger's test if 10 or more studies were included in the meta-analysis of a particular outcome as recommended by the Cochrane handbook.

Results

Results were reported in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Study selection process and description of selected studies

We identified 5473 references during the initial search. Out of these, 5321 articles were excluded because of duplicates publications (Figure 1). The 152 remaining references were further assessed in term of title and abstracts. One hundred and thirty two references were excluded for lack of relevant data. Twenty full text articles were retrieved but 12 articles were excluded for lack of control arm. Eight were included for the data synthesis and meta-analysis.[21–28] The studies included were all randomized control trial (RCTs) published from 2019 to 2023. Five of the studies[21–23,27,28] compared SCS to hypothermic oxygenated perfusion while 3 of the studies[24–26] compared SCS to NMP. Details of selected studies were displayed in Table 1.

Primary outcome

Early allograft dysfunction

The primary outcome we compared was overall Incidence of EAD between the two methods of graft perfusion after liver transplantation. All the eight included studies[21–28] compared the incidence of EAD. In our meta-analysis we found that patients that received liver graft that was preserved with machine perfusion tend to have less incidence of EAD. The difference between the 2 groups was statistically significant with a risk ratio (RR) of 6.48 and a P value of <0.00001. There was no significant heterogeneity between the studies with I^2=0%. (Figure 2A). Publication bias was assessed by visual inspection of funnel plot and it was found to be symmetrical which revealed no bias.

We also performed a subgroup analysis comparing the various methods of machine perfusion to SCS. We found that hypothermic machine perfusion is associated with less EAD when compared to SCS (Figure 2B, RR= 5.31, P<0.0001). Similar finding was also observed when Normothermic machine perfusion was compared to SCS (Figure 2C, RR=3.98, P<0.00001).

Secondary outcome

Post reperfusion syndrome

Four studies[22–25] comprising of 496 patients compared post reperfusion syndrome between the 2 groups of patients. Our pooled meta-analysis revealed that PRS occurred in 92 patients that received liver graft preserved with SCS as opposed to 68 patients whose liver graft were preserved using machine perfusion. This difference was no statistically significant with a RR=0.95 and a P value of 0.34. There is significant heterogeneity among studies included for the meat-analysis with I^2=78% so the random effect was used to estimate pooled effect size. The detailed meta-analysis of post reperfusion syndrome is displayed in figure 3A.

Primary non function and ischemic cholangiopathy

Seven of the studies[21–27] included compared primary non function (PNF) between the 2 methods of liver graft preservation. The pooled sample size of the studies is 523 patients in the machine perfusion group and 494 patients in the SCS group. Pooled analysis revealed that 7 patients had PNF in the SCS group while only 2 patients had PNF in the machine perfusion group. However, this difference was not statistically significant with a RR of 1.41 and a P value of 0.16. There no significant heterogeneity between the included studies with an I^2=0%. The detailed meta-analysis of PNF is displayed in figure 3B.

Ischemic cholangiopathy was compared in only 2 studies[24,25] among included randomized controlled trials. Our pooled analysis showed that 3 out of 111grafts preserved by SCS developed ischemic cholangiopathy as opposed to 2 out of 121 graft preserved with machine perfusion. The difference is not statistically significance with a risk ratio of 0.56 and a p value of 0.57.

Duration of stay in intensive care unit

Five studies[21–23,25,27] consisting 702 patients compared the duration of stay in intensive care unit (ICU) between machine perfusion and SCS of liver graft. Pooled analysis of these studies revealed that the duration of stay in the ICU is similar among the 2 group of patients with mean difference of 0.05 and a P value of 0.96. There was significant heterogeneity among the studies included for the analysis with I^2=57% so the random effect was used in estimating the pooled effect size. The detailed meta-analysis of PNF is displayed in figure 3C.

Retransplantation

Five studies[21–23,25,27] consisting 702 patients compared the rate of retransplantation between machine perfusion and SCS of liver graft. Pooled analysis of these studies revealed that the rate of retransplantation is higher among patients that received liver that was preserved by SCS. The difference was found to be statistically significant with RR of 2.30 and a P value of 0.02. There was no heterogeneity between the studies included for the analysis with I^2=0%. The detailed and graphical representation of this meta-analysis was displayed in figure 4.

Discussion

The increase in demand for liver graft resulted in scarcity of donors and consequently there was increased utilization of extended criteria donors or marginal donors. The definition of marginal donor or extended criteria donor varies but the term is commonly used to describe grafts obtained from donor's age above 65 years, donors that spent at least 7 days in intensive care unit, obese donors, donor with fatty liver, prolonged cold ischemia time for over 12 h, and donors with elevated liver enzymes or hypernatremia at any time.[29,30] There are reports that extended criteria donors may constitute up to 50% of total liver donors in some European countries.[4,31,32] One of the persistent problems that was associated with use of extended criteria donation was that the graft are susceptible to ischemic reperfusion injury which resulted in increased risk of early allograft dysfunction and primary non function.[33–35] These complications predispose the recipients to increased risk of sepsis, increased risk of graft loss and longer stay in the intensive care unit and longer hospital stay.[18]

One of the main aims of machine perfusion is to reduce ischemic reperfusion injury and by extension reduces the risk of early allograft dysfunction and its complication.[18,36] Excellent results have been reported with the use of machine perfusion in preservation of marginal kidney grafts. Initial reports of the use of machine perfusion for graft preservation has also been encouraging with initial reports of reduced risk of ischemic cholangiopathy and graft loss in patients that received machine perfusion when compared to static cold storage.[18,36] In this meta-analysis, we compared early outcome among patients whose graft were preserved by SCS and machine perfusion.

Our meta-analysis revealed that machine preservation of liver graft is associated with reduced risk of early allograft dysfunction when compared to SCS. We also performed a subgroup analysis and we found that both hypothermic machine perfusion and normothermic machine

perfusion are associated with reduced risk of early allograft dysfunction. This is similar to previous meta-analyses of Jia et al[18], Yang et al[36] and Parente et al.[37] The reduction in early allograft dysfunction among grafts that were preserved by machine perfusion may be as result of the reduction of ischemic reperfusion injury after machine preservation. In our meta-analysis, patients whose grafts were preserved with machine perfusion tend to have less post reperfusion syndrome when compared to SCS but the difference was not significant. However, there was marked heterogeneity among the studies included. We also found that there is reduction in primary non function among graft that was preserved with machine perfusion but when compared with SCS, the difference was not statistically significant. These are similar to the findings of Jia et al[18] and Parente et al.[37]

Retransplantation after liver transplantation is a dreaded complication and it may be due multitude of factors ranging from vascular complications, technical issues, immunological tissue, allograft dysfunction or non-function.[38,39] In this meta-analysis, we found that the rate of retransplantation is higher among patients that had SCS preservation of their liver graft. This may be related to increased risk of early allograft dysfunction and the trend of Primary non function to occur in this group of patients. The same results were reported by Yang et al[36] and Parente et al.[37]

Some of the limitations of this meta-analysis include the fact that some studies have small sample sizes which make them susceptible to higher risks of bias. Also the fact that only studies published in English, there is a potential for overlooking studies not published in English.

Conclusion

The use of machine perfusion in preservation of liver graft showed significant reduction in early allograft dysfunction and retransplantation when compared to static cold storage and preservation.

Acknowledgement

The authors want to acknowledge the management and staff of XXXXXXXXXXXXXXXXX for their contribution during literature search and analysis.

References

1. Jiménez-Romero C. Using old liver grafts for liver transplantation: Where are the limits? World J Gastroenterol [Internet] 2014;20(31):10691. Available from: http://www.wjgnet.com/1007-9327/full/v20/i31/10691.htm

2. Patrono D, De Stefano N, Vissio E, Apostu AL, Petronio N, Vitelli G, et al. How to Preserve Steatotic Liver Grafts for Transplantation. J Clin Med [Internet] 2023;12(12):3982. Available from: https://www.mdpi.com/2077-0383/12/12/3982

3. Goldaracena N, Cullen JM, Kim D-S, Ekser B, Halazun KJ. Expanding the donor pool for liver transplantation with marginal donors. Int J Surg [Internet] 2020;82:30–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1743919120304076

4. Widmer J, Eden J, Carvalho MF, Dutkowski P, Schlegel A. Machine Perfusion for Extended Criteria Donor Livers: What Challenges Remain? J Clin Med [Internet] 2022;11(17):5218. Available from: https://www.mdpi.com/2077-0383/11/17/5218

5. Neves DB, Rusi MB, Diaz LGG, Salvalaggio P. Primary graft dysfunction of the liver: definitions, diagnostic criteria and risk factors. Einstein (São Paulo) [Internet]

2016;14(4):567–72. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1679-45082016000400567&lng=en&tlng=en

6. Malkawi D, Savsani K, Alfonso A, Lee SD, James N, Sarkar D, et al. The Role of Normothermic Machine Perfusion in Extended Criteria Donor Grafts: A New Direction in Liver Graft Assessment and Preservation. Livers [Internet] 2023;3(4):709–26. Available from: https://www.mdpi.com/2673-4389/3/4/46

7. Ahmed E, El-Badry A, Mocchegiani F, Montalti R, Hassan A, Redwan A, et al. Impact of Graft Steatosis on Postoperative Complications after Liver Transplantation. Surg J [Internet] 2018;04(04):e188–96. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0038-1675236

8. Liu J, Man K. Mechanistic Insight and Clinical Implications of Ischemia/Reperfusion Injury Post Liver Transplantation. Cell Mol Gastroenterol Hepatol [Internet] 2023;15(6):1463–74. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2352345X23000401

9. Obed A, Alsakarneh S, Abuassi M, Bashir A, Ahmad BA, Jarrad A, et al. Ischemic Reperfusion Injury After Liver Transplantation: Is There a Place for Conservative Management? Gastroenterol Res [Internet] 2023;16(1):50–5. Available from: http://www.gastrores.org/index.php/Gastrores/article/view/1584

10. Rampes S, Ma D. Hepatic ischemia-reperfusion injury in liver transplant setting: mechanisms and protective strategies. J Biomed Res [Internet] 2019;33(4):221. Available from: http://www.jbr-pub.org.cn/article/doi/10.7555/JBR.32.20180087?viewType=HTML

11. Halazun KJ, Al-Mukhtar A, Aldouri A, Willis S, Ahmad N. Warm Ischemia in Transplantation: Search for a Consensus Definition. Transplant Proc [Internet] 2007;39(5):1329–31. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0041134507002771

12. Soares ROS, Losada DM, Jordani MC, Évora P, Castro-e-Silva O. Ischemia/Reperfusion Injury Revisited: An Overview of the Latest Pharmacological Strategies. Int J Mol Sci [Internet] 2019;20(20):5034. Available from: https://www.mdpi.com/1422-0067/20/20/5034

13. Czigany Z, Lurje I, Schmelzle M, Schöning W, Öllinger R, Raschzok N, et al. Ischemia-Reperfusion Injury in Marginal Liver Grafts and the Role of Hypothermic Machine Perfusion: Molecular Mechanisms and Clinical Implications. J Clin Med [Internet] 2020;9(3):846. Available from: https://www.mdpi.com/2077-0383/9/3/846

14. Pradat P, Pantel S, Maynard M, Lalande L, Thevenon S, Adam R, et al. End-ischemic hypothermic oxygenated perfusion for extended criteria donors in liver transplantation: a multicenter, randomized controlled trial—HOPExt. Trials [Internet] 2023;24(1):379. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-023-07402-0

15. Tchilikidi KY. Liver graft preservation methods during cold ischemia phase and normothermic machine perfusion. World J Gastrointest Surg [Internet] 2019;11(3):126–42. Available from: https://www.wjgnet.com/1948-9366/full/v11/i3/126.htm

16. Schlegel A, Mergental H, Fondevila C, Porte RJ, Friend PJ, Dutkowski P. Machine perfusion of the liver and bioengineering. J Hepatol [Internet] 2023;78(6):1181–98.

Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168827823000971

17. Brüggenwirth IMA, van Leeuwen OB, de Vries Y, Bodewes SB, Adelmeijer J, Wiersema-Buist J, et al. Extended hypothermic oxygenated machine perfusion enables ex situ preservation of porcine livers for up to 24 hours. JHEP Reports [Internet] 2020;2(2):100092. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2589555920300264

18. Jia J, Nie Y, Li J, Xie H, Zhou L, Yu J, et al. A Systematic Review and Meta-Analysis of Machine Perfusion vs. Static Cold Storage of Liver Allografts on Liver Transplantation Outcomes: The Future Direction of Graft Preservation. Front Med [Internet] 2020;7. Available from: https://www.frontiersin.org/article/10.3389/fmed.2020.00135/full

19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials [Internet] 1996;17(1):1–12. Available from: https://linkinghub.elsevier.com/retrieve/pii/0197245695001344

20. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14(1).

21. Schlegel A, Mueller M, Muller X, Eden J, Panconesi R, von Felten S, et al. A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation. J Hepatol [Internet] 2023;78(4):783–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168827823000120

22. van Rijn R, Schurink IJ, de Vries Y, van den Berg AP, Cortes Cerisuelo M, Darwish Murad S, et al. Hypothermic Machine Perfusion in Liver Transplantation — A Randomized Trial. N Engl J Med [Internet] 2021;384(15):1391–401. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2031532

23. Ravaioli M, Germinario G, Dajti G, Sessa M, Vasuri F, Siniscalchi A, et al. Hypothermic oxygenated perfusion in extended criteria donor liver transplantation—A randomized clinical trial. Am J Transplant [Internet] 2022;22(10):2401–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1600613522299432

24. Ghinolfi D, Rreka E, De Tata V, Franzini M, Pezzati D, Fierabracci V, et al. Pilot, Open, Randomized, Prospective Trial for Normothermic Machine Perfusion Evaluation in Liver Transplantation From Older Donors. Liver Transplant [Internet] 2019;25(3):436–49. Available from: https://journals.lww.com/01445473-201903000-00014

25. Nasralla D, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, et al. A randomized trial of normothermic preservation in liver transplantation. Nature [Internet] 2018;557(7703):50–6. Available from: https://www.nature.com/articles/s41586-018-0047-9

26. Markmann JF, Abouljoud MS, Ghobrial RM, Bhati CS, Pelletier SJ, Lu AD, et al. Impact of Portable Normothermic Blood-Based Machine Perfusion on Outcomes of Liver Transplant. JAMA Surg [Internet] 2022;157(3):189. Available from: https://jamanetwork.com/journals/jamasurgery/fullarticle/2787486

27. Czigany Z, Pratschke J, Fron□k J, Guba M, Schöning W, Raptis DA, et al. Hypothermic Oxygenated Machine Perfusion Reduces Early Allograft Injury and Improves Post-

transplant Outcomes in Extended Criteria Donation Liver Transplantation From Donation After Brain Death. Ann Surg [Internet] 2021;274(5):705–12. Available from: https://journals.lww.com/10.1097/SLA.0000000000005110

28. Gr□t M, Morawski M, Zhylko A, Rykowski P, Krasnod□bski M, Wyporski A, et al. Routine End-ischemic Hypothermic Oxygenated Machine Perfusion in Liver Transplantation From Donors After Brain Death. Ann Surg [Internet] 2023;278(5):662–8. Available from: https://journals.lww.com/10.1097/SLA.0000000000006055

29. Nair A, Hashimoto K. Extended criteria donors in liver transplantation—from marginality to mainstream. HepatoBiliary Surg Nutr [Internet] 2018;7(5):386–8. Available from: http://hbsn.amegroups.com/article/view/20279/21146

30. Lozanovski V, Kerr L, Khajeh E, Ghamarnejad O, Pfeiffenberger J, Hoffmann K, et al. Liver Grafts with Major Extended Donor Criteria May Expand the Organ Pool for Patients with Hepatocellular Carcinoma. J Clin Med [Internet] 2019;8(10):1692. Available from: https://www.mdpi.com/2077-0383/8/10/1692

31. Durand F, Renz JF, Alkofer B, Burra P, Clavien P-A, Porte RJ, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. Liver Transplant [Internet] 2008;14(12):1694–707. Available from: https://onlinelibrary.wiley.com/doi/10.1002/lt.21668

32. METİN O, ŞİMŞEK C, GÜRAKAR A. Update on liver transplantation-newer aspects. TURKISH J Med Sci [Internet] 2020;50(7):1642–50. Available from: https://journals.tubitak.gov.tr/medical/vol50/iss10/7

33. Agostini C, Buccianti S, Risaliti M, Fortuna L, Tirloni L, Tucci R, et al. Complications in Post-Liver Transplant Patients. J Clin Med [Internet] 2023;12(19):6173. Available from: https://www.mdpi.com/2077-0383/12/19/6173

34. Dery KJ, Yao S, Cheng B, Kupiec-Weglinski JW. New therapeutic concepts against ischemia-reperfusion injury in organ transplantation. Expert Rev Clin Immunol [Internet] 2023;19(10):1205–24. Available from: https://www.tandfonline.com/doi/full/10.1080/1744666X.2023.2240516

35. Cursio R, Gugenheim J. Ischemia-Reperfusion Injury and Ischemic-Type Biliary Lesions following Liver Transplantation. J Transplant [Internet] 2012;2012:1–17. Available from: http://www.hindawi.com/journals/jtrans/2012/164329/

36. Yang X, Li Y, Guo Q, Li Y, Zhong X. Effectiveness of machine perfusion in liver transplantation: A meta-analysis of randomized controlled trials. J Liver Transplant [Internet] 2023;12:100176. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2666967623000387

37. Parente A, Tirotta F, Pini A, Eden J, Dondossola D, Manzia TM, et al. Machine perfusion techniques for liver transplantation - A meta-analysis of the first seven randomized-controlled trials. J Hepatol [Internet] 2023;79(5):1201–13. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168827823003999

38. Bekker J, Ploem S, De Jong KP. Early Hepatic Artery Thrombosis after Liver Transplantation: A Systematic Review of the Incidence, Outcome and Risk Factors. Am J Transplant [Internet] 2009;9(4):746–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1600613522016355

39. Piardi T. Vascular complications following liver transplantation: A literature review of advances in 2015. World J Hepatol [Internet] 2016;8(1):36. Available from: http://www.wjgnet.com/1948-5182/full/v8/i1/36.htm

S/N	Author	Year of publication	Sample size per group		Jadad Score	Quality of the study
			SCS*	MP[ŧ]		
1	Schlegel et al	2023	85	85	4	Good quality
2	Van Rijn et al	2021	78	78	4	Good quality
3	Ravaioli et al	2022	55	55	4	Good quality
4	Ghinolfi et al	2019	10	10	4	Good quality
5	Markman et al	2022	142	151	3	Good quality
6	Czigany et al	2021	23	23	4	Good quality
7	Grat et al	2023	78	26	3	Good quality
8	Nasralla et al	2019	101	121	3	Good quality

***SCS: Static cold storage**
[ŧ]MP: Machine perfusion

Table 1: Characteristics of included studies

Figure legends

Fig 1: Study selection process

Fig 2: A. Meta-analysis comparing early allograft dysfunction between MP and SCS

B. A. Meta-analysis comparing early allograft dysfunction between HMP and SCS

C. A. Meta-analysis comparing early allograft dysfunction between NMP and SCS

Fig 3: A. Meta-analysis comparing post reperfusion syndrome between MP and SCS

B. A. Meta-analysis comparing primary non-function between HMP and SCS

C. A. Meta-analysis comparing ICU stay between NMP and SCS

Fig 4: Meta-analysis comparing retransplantation between MP and SCS