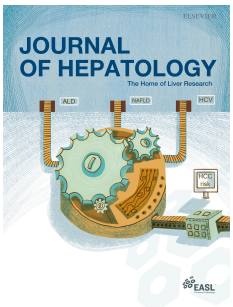
Journal Pre-proof



L-GrAFT and EASE scores in liver transplantation. Need for a reciprocal external validation and comparison with other scores.

Alfonso W. Avolio, MD, Quirino Lai, MD, PhD, Umberto Cillo, MD, Renato Romagnoli, MD, Paolo De Simone, MD, PhD

PII: S0168-8278(20)33848-4

DOI: https://doi.org/10.1016/j.jhep.2020.12.009

Reference: JHEPAT 8066

To appear in: *Journal of Hepatology*

Received Date: 22 October 2020

Revised Date: 7 December 2020

Accepted Date: 10 December 2020

Please cite this article as: Avolio AW, Lai Q, Cillo U, Romagnoli R, De Simone P, L-GrAFT and EASE scores in liver transplantation. Need for a reciprocal external validation and comparison with other scores., *Journal of Hepatology* (2021), doi: https://doi.org/10.1016/j.jhep.2020.12.009.

L-GrAFT and EASE scores in liver transplantation. Need for a reciprocal external validation and comparison with other scores.

Alfonso W Avolio[1,2*] MD; ORCID 0000-0003-2491-7625
Quirino Lai[3] MD, PhD; ORCID 0000-0003-1487-3235
Umberto Cillo[4] MD; ORCID 0000-0002-2310-0245
Renato Romagnoli[5] MD; ORCID 0000-0001-8340-8885
and
Paolo De Simone[6] MD, PhD; MD, ORCID 0000-0001-6713-6170

[1]General Surgery and Liver Transplantaion Unit
Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome (IT)
[2]Università Cattolica del Sacro Cuore, Rome (IT)
[3]General Surgery and Transplantation Unit, Policlinico Universitario Umberto I, Rome (IT)
[4]Hepatobiliary Surgery and Liver Transplantation Unit, University Hospital, Padua (IT)
[5]General Surgery and Liver Transplant Unit, Molinette University Hospital, Turin (IT)
[6]Hepatobiliary Surgery and Liver Transplantation, University Hospital Pisa (IT)

Corresponding Author: [1,2]Alfonso W. Avolio, alfonso.avolio@unicatt.it
Dept of Surgery, General Surgery and Liver Transplant Unit
Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome (IT)

ClinicalTrials.gov (NCT03858088)
Total number of words of the manuscript: 797; Total number of Tables: 3 (1 Table, 2 Supplementary Tables)
Keywords: Liver transplantation, Early Allograft Failure, Primary non-function, Primary dysfunction, Delayed non-function, Prognostic Score, EASE score, Smartphone Calculator.
Outcome, Re-transplant, Unsustainable-risk class, DCD, Machine Perfusion.

Conflict of interest. The authors declare no conflicts of interest that pertain to this work.
Author contribution. AWA and QL wrote the letter, UC, RR and PDS revised and approved the final version of the letter.
Financial support. The authors received no financial support to produce this manuscript.
Data availability. The data that support the findings of this study are available from the corresponding author, upon request.
Supplementary data. Supplementary data (Supplementary sTable 1 and Supplementary sTable 2) to this article can be found online at …

Dear Editor,

We read with great interest the recent article by Agopian et al. on the validation of the Liver Graft Assessment Following Transplantation (L-GrAFT) score for prediction of Early Allograft Failure (EAF).[1] EAF was defined as the failure of the graft (identified by retransplant or death) for any reason at 90 days after liver transplantation.[1-2] Adopting an innovative "kinetic" approach which included calculation of the area under the curve (AUC) and slope of AST, bilirubin, platelet count, and international normalized ratio (INR), the L-GrAFT[1-2] was reported to outperform both the Model for Early Allograft Function (MEAF)[3] and Early Allograft Dysfunction (EAD)[34] scores, namely the strongest validated scores available to date in this setting. The authors used a cumulative retrospective database from four North American (n=3201) and seven European (n=222) large volume centers.[1] The L-GrAFT has two calculation modalities: at seven days ($L\text{-}GrAFT_7$) and at ten days ($L\text{-}GrAFT_{10}$). Twenty-eight and 40 data entries are needed for calculating the scores, respectively. Both L-GrAFT scores were validated in the US cohort, while only the score at seven days was validated in the European cohort. For the $L\text{-}GrAFT_7$, the authors report a C-statistic of 0.78 and 0.82 in the US and European cohort, respectively. Unfortunately, calculation of L-GrAFT scores is rather complex due to the significant number of requested data entries and their estimation intrinsic nature. Moreover, a dedicated software is not yet available, and its logarithmic transformation does not help daily use.

On these bases, we here provide a counterpoint to L-GrAFT offering additional evidence about early liver graft dysfunction prediction. Starting from the seminal study by Agopian,[1] we have recently validated the $L\text{-}GrAFT_{10}$ on a population of 1,609 patients transplanted between 2016 and 2017 in 14 Italian centers and obtained a C-statistic of 0.72.[5] Using the original L-GrAFT components, we have further refined and simplified the $L\text{-}GrAFT_{10}$ formula reducing the number of data entries from 40 to 17. The beta-coefficients were re-calculated, and additional donor and recipient parameters were tested in eight models. The final comprehensive score for EAF assessment, namely Early Allograft failure Simplified Estimation (EASE) score, was internally validated through bootstrap and externally validated on a UK database (2 centers, 570 patients). The characteristics of both databases and the EASE-score formula are reported in the supplementary online sTable 1 and sTable 2 respectively. Notably, the overall prevalence of grafts from donors after cardiac death (DCD) and machine perfused (MP) grafts was 6.8% and 5.8%, respectively. Because both these categories

were not significant predictors, EASE is a precise algorithm to measure graft quality in also translational studies including DCD and MP high-risk grafts.

Unlike L-GrAFT$_{10}$, the EASE score does not include INR. Its AUC and slope are based on a lower number of evaluations (4 versus 10), and no logarithmic transformation was used for bilirubin. Furthermore, the EASE score includes the following, easy-to-be-retrieved additional parameters: MELD at transplant, number of intraoperatively transfused packed red blood cells (PRBC), hepatic vessel thrombosis on day 10, and center volume (≥70 or between 36 and 69 cases per year).

As a result, the EASE achieved a C-statistic of 0.87 (95%CI=0,83-0,91) in the derivation set and outperformed all previously developed scores to predict EAF (Table 1).[1-4,6-9] With respect to the comparison with the L-GrAFT (C-statistic 0.72; 95%CI=0,65-078), the difference resulted significant at the DeLong test.[10] Although one could argue that a researcher-derived bias cannot be excluded, we invite the L-GrAFT developers to test the EASE on both the North-American and COPE databases.

The EASE also showed excellent C-statistic (0.93; 95%CI 0.89-0.97) for prediction of EAF at 30 days and was further validated in the UK cohort with a C-statistic of 0.78. Furthermore, it allows stratification of liver grafts in five classes, with the highest one including cases to be referred to early retransplantation. The online EASE-score calculator is available at https://oaa.app.link/d/HF368te2nbb

Listing a patient for retransplant is often challenging, and surgeons and transplant hepatologists are frequently reluctant in the absence of objective signs of graft failure. In our opinion, the inclusion of MELD, PRBC, and hepatic vessel thrombosis is essential for an innovative and comprehensive definition of EAF. Notably, thrombosis of a hepatic vessel is a well-known indication of early retransplant. However, medical and endovascular treatments of thrombosis are now more efficacious than in the past, and several patients without associated liver failure recover. In this perspective, parenchymal and vascular causes of failure are linked in an innovative definition of EAF and share the same retransplant treatment. Prediction of 90-day outcome and early identification of patients in need of retransplantation remain a priority. The choice of the best algorithm requires multiple external validation studies. A further step could be to design a prospective international validation study to enroll a larger number of cases and including small-volume center series.

References

1. Agopian VG, Markovic D, Klintmalm GB, Saracino G, Chapman WC, Vachharajani N, et al. Multicenter validation of the liver graft assessment following transplantation (L-GrAFT) score for the assessment of early allograft dysfunction. J Hepatol. 2020 Sep 22:S0168-8278(20)33627-8. doi: 10.1016/j.jhep.2020.09.015. Epub ahead of print.
2. Agopian VG, Harlander-Locke MP, Markovic D, Dumronggittigule W, Xia V, Kaldas FM et al. Evaluation of Early allograft Function Using the Liver Graft Assessment Following Transplantation Risk Score Model. JAMA Surg 2018;153:436-444.
3. Pareja E, Cortes M, Hervás D, Mir J, Valdivieso A, Castell JV, et al. A score model for the continuous grading of early allograft dysfunction severity. Liver Transpl 2015;21:38-46.
4. Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl 2010;16:943-949.
5. Avolio AW, Franco A, Schlegel A, Lai Q, Meli S, Burra P et al. Development and validation of a comprehensive model to estimate early allograft failure among patients requiring early liver retransplant. Jama Surg. Published online October 28, 2020. doi: 10.1001/jamasurg.2020.4095 Epub ahead of print.
6. Avolio AW, Agnes S, Cillo U, Lirosi MC, Romagnoli R, Baccarani U, et al. http://www.DMELD.com, the Italian survival calculator to optimize donor to recipient matching and to identify the unsustainable matches in liver transplantation. Transpl Int 2012;25:294-301.
7. Avolio AW, Cillo U, Salizzoni M, De Carlis L, Colledan M, Gerunda GE, et al. Balancing donor and recipient risk factors in liver transplantation: the value of D-MELD with particular reference to HCV recipients. Am J Transplant 2011;11:2724-2736.
8. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am J Transplant 2012;12:2789-2796.
9. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 2006;6:783-790.
10. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-45.

Table 1. Comparison between EASE-score and other prognostic scores predictive of EAF.

	C-statistic	95% CI	p-value
EASE-score *(reference)*	0,87	0,83-0,91	
DRI[9]	0,53	0,46-0,59	<0,001
EAD[4]	0,70	0,63-0,75	<0,001
D-MELD[6]	0,60	0,54-0,67	<0,001
New ET-DRI[8]	0,55	0,49-0,62	<0,001
MEAF[3]	0,73	0,67-0,79	<0,001
L-GrAFT$_{10}$[2]	0,72	0,65-0,78	<0,001

Abbreviations. DRI, Donor Risk Index; EAD, Early Allograft Dysfunction score; D-MELD, Donor age x MELD score; New ET-DRI, New Euro-Transplant Donor Risk Index; MEAF, Model for Early Allograft Failure score; L-GrAFT$_{10}$, Liver Graft Assessment Following Transplantation.

Notes. EASE score shows the highest C-statistic at 90 days. The P values refer to the comparison of the indicated score against EASE-score. EASE-score has a high discrimination ability (absence of overlap of 95% CI between EASE score and other scores).