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# The efficacy of two models – MEAF and pMELD, as indicators of lethal outcome in early postoperative period after liver transplantation in children



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## ABSTRACT

Early allograft dysfunction following liver transplantation is a clinical entity that represents a condition in which the liver graft shows some degree of hepatic injury, but the functions are sufficient to support life. Many models have been developed to individualize the risk of transplant failure that include parameters that are significantly associated with allograft dysfunction.

**THE PURPOSE.** The current study is aiming to prove the effectiveness and compare “Model for Early Allograft Function” (MEAF) and “postoperative Model for End-stage Liver Disease” (pMELD) in the early post-transplant setting in children.

**METHODS.** We carried out a retrospective study on 43 liver transplant patients for a 17-year period between the ages 0-18 years. MEAF and pMELD were calculated on the third and fifth postoperative day, respectively, and a Cox regression analysis was performed to find the correlation between them and mortality in the early postoperative period.

**RESULTS.** Both scores proved to be statistically significant and applicable in early postoperative period. MEAF had *p* value of 0.0003 and a hazard ratio of 10.99, while pMELD demonstrated *p* value of 0.003 and a hazard ratio of 1.24.

**CONCLUSIONS.** Both MEAF and pMELD can be used for the diagnostics of early allograft dysfunction and predicting the outcome of the liver transplantation in children, with MEAF having the upper hand.

**KEY WORDS:** pediatric liver transplantation; early allograft dysfunction; graft survival

The success of liver transplantation (LT) in the last decade is enviable. It is the result of the improvement of surgical techniques, progress in immunosuppressive therapy, accumulated experience in the perioperative care of transplanted patients, etc. Predicting post-liver transplantation complications already in the first days after surgery is important for the outcome of LT. Accurate assessment of graft function can help clinicians make sufficiently early decisions, incl. the benefit of retransplantation.

Early allograft dysfunction (EAD) following LT is a clinical entity that represents a condition in which the liver graft shows some degree of hepatic injury, but the functions are sufficient to support life. EAD is of some significance, which is believed to impact long-term patient and graft survival [1]. However, a widely accepted classification or grading system is lacking. There are many definitions of EAD, but the one created by Olthoff et al. is the most widely used: (1) bilirubin  $\geq 10$  mg/dL on the post-operation day (POD) 7; (2) international normalized ratio (INR)  $\geq 1.6$  on POD 7;

and (3) alanine aminotransferases (ALT) or aspartate aminotransferases (AST)  $> 2,000$  IU/L within the first 7 days [2].

Many models have been developed to individualize the risk of transplant failure that include parameters that are significantly associated with EAD. Pareja et al. created a continuous score model called the Model for Early Allograft Function (MEAF) scoring to evaluate EAD. The scoring is based on graft survival at different intervals and is made by a calculation containing ALT, INR and total bilirubin on the 3<sup>rd</sup> postoperative day [3]. Agopian et al. created a new continuous score model called Liver Graft Assessment Following Transplantation (L-GrAFT) risk score, which uses 7- or 10-days post-operative laboratory variables – ALT, INR, total bilirubin (TBIL), and platelets (PLT) – to calculate the risk score and evaluate the graft failure risk [4]. Avolio et al. created a model called the Early Allograft failure Simplified Estimation (EASE) score to evaluate the early allograft failure. The EASE score was developed through 17 entries derived

from 8 variables, including the Model for End-stage Liver Disease (MELD) score, blood transfusion, early thrombosis of hepatic vessels, and kinetic parameters of transaminases, platelets count, and bilirubin [5]. Postoperative Model for End-Stage Liver Disease (pMELD) was also analyzed as a predictor of mortality in a constructed logistic model [6, 7].

**THE PURPOSE** of this study is to confirm the efficacy of two models – MEAF and pMELD, as indicators of lethal outcome in early postoperative period (EPOP) after liver transplantation in children as well as to compare the predictive power of the two models. This retrospective single-center analysis used a database of transplants at Lozenetz University Hospital, Sofia, Bulgaria.

## MATERIALS AND METHODS

**Recipients population and clinical data collection.** Our study cohort included all consecutive LTs performed at Lozenetz University Hospital from January 1, 2005 to January 31, 2022 for patients on waiting list. This was done in accordance with the MELD and Pediatric End-Stage Liver Disease (PELD) scores and in agreement with our Executive Agency Medical Supervision and after the patient and their parents' consent had been obtained. Our study enrolled 43 recipients. The mean age was 4 years, with ages ranging from 3 months to 17 years. Females slightly predominated (58 %). The most common primary diagnoses for end-stage liver disease in the cohort study were biliary atresia (48 %), progressive familial intrahepatic cholestasis (14 %), autoimmune hepatitis (7 %), Budd-Chiari syndrome (7 %). The patients' mean PELD/MELD score was 20 with 3 patients placed in the waiting list as status 1A.

**Donor Population.** The donors were living and cadaveric. ABO blood group compatibility and relative size matching between donors and recipients were required. Cadaveric donors were accepted after brain death. Donor livers with fatty infiltration (macrovesicular steatosis with more than 40 % involvement) were declined.

**Models.** We used two models for prediction of mortality after pediatric liver transplantation: Model for Early Allograft Function (MEAF) and Model for End-Stage Liver Disease in the post-transplant period (pMELD). The parameters evaluating the function of the grafted liver after LT were obtained by biochemical examination. Blood samples were collected once per day from post-LT days 1 to 7.

MEAF was calculated on the third day using the following formula (3):

$$\text{scoreALT}_{\text{max.3POD}} + \text{scoreINR}_{\text{max.3POD}} + \text{bilirubinmax}_{\text{3,POD}}$$

with each of these variables calculated individually by these formulas:

$$\text{scoreALT}_{\text{max.3POD}} = \frac{3.29}{1 + e^{-1.9132}}$$

$$\text{scoreINR}_{\text{max.3POD}} = \frac{3.29}{1 + e^{-6.8204}}$$

$$\text{scorebilirubinmax}_{\text{3,POD}} = \frac{3.29}{1 + e^{-1.8005}}$$

Postoperative MELD was calculated using the following formula on the fifth postoperative day [8]:

$$\text{MELD}(i) = 0.957 \times \ln(\text{Cr}) + 0.378 \times \ln(\text{bilirubin}) + 1.120 \times \ln(\text{INR}) + 0.643$$

The results were then rounded to the tenth decimal place and multiplied by 10. If MELD(i) was more than 11 we performed an additional MELD calculation including sodium (Na) as follows:

$$\text{MELD} = \text{MELD}(i) + 1.32 \times (137 - \text{Na}) - [0.033 \times \text{MELD}(i) \times (137 - \text{Na})]$$

**Statistical analysis.** Cox proportional regression analysis is applied to study the association of two independent risk factors on survival of patients after the liver transplantation: MEAF (a Model for Early Allograft Function) denoted as  $X_1$  and pMELD (a Model for End-Stage Liver Disease) denoted as  $X_2$ . These factors are considered simultaneously. There are three important assumptions for the appropriate use of the Cox proportional hazards regression model, namely the independence of survival times between distinct individuals in the sample, multiplicative relationship between the predictors and the hazard and constant hazard ratio over time. Thus, the Cox proportional hazards regression model may be written as:

$$h(t) = h_0(t) \exp(b_1 X_1 + b_2 X_2),$$

where  $h(t)$  is the expected hazard at time  $t$ ,  $h_0(t)$  is the baseline hazard and represents the hazard when  $X_1 = 0$  and  $X_2 = 0$ .

Suppose that we wish to compare two participants in terms of their expected hazards, and the first has  $X_1 = A$  and the second has  $X_1 = B$ . The expected hazards are  $h_0(t) \exp(b_1 A)$  and  $h_0(t) \exp(b_1 B)$ . The hazard ratio is the ratio of these two expected hazards,  $\exp(b_1(A - B))$ , which does not depend on time.

The estimated coefficient  $b_1$  represents the change in the expected logarithm of the hazard ratio relative to a one-unit change in  $X_1$ , keeping  $X_2$  constant. The quantity  $\exp(bk)$  produces a hazard ratio. If a predictor is dichotomous, this quantity is the hazard ratio comparing the risk of event for participants with  $X_1 = 1$  to participants with  $X_1 = 0$ .

If the hazard ratio for a predictor is close to 1, that predictor does not affect survival. If the hazard ratio is less than 1, the predictor is associated with improved survival, and if the hazard ratio is greater than 1, the predictor is associated with increased risk [9].

## RESULTS AND DISCUSSION

The MEAF score calculated for our population ranged from 2.7 to 9.7 (**Fig. 1**) with 14 patients (32 %) having MEAF score above 8. Results from the pMELD calculation ranged from 7 to 39 (**Fig. 2**) with the majority of recipients having scores between 20 and 30 (53 %).

The association between the MEAF score and patient survival was examined with a Cox regression analysis. Among the 43 recipients enrolled in our study, 8 patients died from causes related to OLT at the 1-month follow-up. The survival analysis showed a significant association between the MEAF score and mortality during the first month ( $p=0.0003$ ). The estimated hazard ratio was 10.99 with 95 % confidence interval (CI): 3.04 - 39.81 (**Table 1**). The mortality rate rose to 43 % for the recipients with MEAF scores >8. With respect to graft survival, 1 recipient underwent retransplantation during the first postoperative month.

Postoperative MELD has a hazard ratio of 1.24 with CI of 1.07 to 1.42 and shows statistical significance ( $p = 0.003$ ) with its correlation with lethality during the EPOP. Although the hazard ratio is significantly lower than in MEAF, this variable has higher range and narrower CI which can be useful. Patients with lethal outcome are exclusive with scores above 20 and scores above 30 proved to be a good predictor for negative outcome as 80 % of the cases with scores above 30 had negative outcomes.

Based on the results shown in **Table 1**, both MEAF and pMELD had good predictive value for mortality and graft survival. pMELD calculated on the 5<sup>th</sup> postoperative day has comparable value to the MEAF score with easy-to-use variables.

Pediatric LT has become the effective treatment for acute liver failure and end-stage liver diseases. The number of LT in children has been increasing everywhere in the world. This leads to a reduction in mortality among pediatric patients with severe liver damage while they are waiting for their new organ. There is a multitude of reasons for this success, but two of them should be noted: expanding the indications and reducing the contraindications for LT and using living donor LT in children. Using the extended donor criteria for liver allografts also contributes to reducing

mortality in the waiting list, but at the price of more complications after the surgery. Some of the more severe and impactful complications are EAD, primary nonfunction (PNF) and death during the first postoperative week. That is why it is extremely important to be able to predict EAD and develop a model that foresees lethal outcome in the EPOP.

Historically there were numerous criteria trying to evaluate early allograft dysfunction and its effect on graft survival and mortality in both the early and late postoperative period. Most of these scores were based on different laboratory values as they are easy to both get and evaluate. There are some modern score systems like the L-GRAFT and EASE scores which also try to include variables such as mechanical ventilation, dialysis, platelets count, blood transfusions and more, but these systems are harder to implement and they have also not been well proven for pediatric patients. MEAF and pMELD are easy to calculate as they use common variables and have almost the same impact on graft survival outcomes.

Postoperative MELD has been partially evaluated as a predictor of unfavorable outcome after LT and can help in assessing the need for retransplantation. Uzunova et al. published results of a retrospective study of 27 liver transplant children using pMELD as a predictor of lethal outcome after liver transplantation. A univariate analysis was used and the logistic model using pMELD was constructed on postoperative day 5, which predicted disadvantageous outcome after LT with good statistical significance ( $p < 0.05$ ).

Jochmans et al. proved that the MEAF score was a superior predictor of transplant loss than the criteria set by Olthoff in 2010 [10]. Their research included 660 liver transplantations on adult patients of similar age, MELD score and cold ischemia times. They proved that early allograft dysfunction is an independent factor on graft survival at 3, 6 and 12 months after LT. The cutoffs they managed to evaluate for MEAF were 5, 8 and 10 with severe mortality in the patients with scores of 8 and 10. In this research we have found that scores above 8 for MEAF prove to be the most significant regarding EAD, graft and patient survival.

A lot of studies [10-12] have found that even when Olthoff and MEAF scores overlap in the diagnosis of EAD, MEAF is still superior due to the fact that it is calculated on the 3<sup>rd</sup> day, while Olthoff criteria can be evaluated on the 7<sup>th</sup> postoperative day. Early diagnosis of moderate to severe EAD using MEAF tends to be very useful as centers will reassess those patients and search for possible reasons for graft malfunction and provide earlier treatment if possible. Also scores above 8 tend to be associated with high possibility of the graft loss and the transplant center can arrange some preparations if retransplant is needed. Our cohort of patients demonstrates this, as patients with scores more than 8 have 43 % mortality rate and early reevaluation can prove to be beneficial as retransplantation can be done in timely manner.

Staging of the severity of dysfunction is an entity that has been barely touched in previous researches. There are definitions such as Ardite from 1999 [13] and Dhillon from 2010 [14] that try to separate patients with different stages of EAD, but these scores have been abandoned due to their inconsistencies. MEAF is the first score that manages to grade patients after LT and is able to make a better prognosis for graft failure based on its values. We compared MEAF scores between 0 and 6, 6 and 8 and above 8 and found that those groups have different mean survival rates with high statistical significance ( $p < 0.05$ ). Patients with MEAF scores from 0 to 8 tend to survive the EPOP and only 2 patients (4.6 %) had unfavorable outcome in the first month after LT.

A problem in applying different EAD definition in the pediatric population is the lack of conformational studies for children for a lot of these scores. That is why in pediatric LT most centers continue to use the Olthoff criteria as it has been proven to work for these patients. There is a need for better analysis of scores such as MEAF and our retrospective study, although with a small cohort proves the significance of both MEAF and pMELD and its efficacy in diagnosing EAD in pediatric patients.

## CONCLUSION

*In conclusion, MEAF and pMELD are both usable in the post-transplant setting after pediatric liver transplantation with each having its own merits. MEAF has the ability to separate patients in groups based on the severity of early allograft dysfunction and can make a better prognosis of the outcome based on that. pMELD proved to be statistically significant across this research and it would be beneficial to create another study assessing different cutoff values to better discriminate between different severities of dysfunction.*

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## Ефективність моделей MEAF та rMELD як показників летального результату в ранньому післяопераційному періоді після трансплантації печінки у дітей



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### РЕЗЮМЕ

Рання дисфункція алотрансплантата після трансплантації печінки є клінічним станом, при якому трансплантат має певний ступінь пошкодження, але його функції є достатніми для підтримки життя. Відомо багато моделей для індивідуалізації ризику невдачі трансплантації, які включають параметри оцінки, що значною мірою пов'язані з дисфункцією алотрансплантата.

**МЕТОЮ ДОСЛІДЖЕННЯ** було довести ефективність і порівняти модель ранньої функції алотрансплантата (Model for Early Allograft Function – MEAF) і післяопераційну модель термінальної стадії захворювання печінки (postoperative Model for End-stage Liver Disease – rMELD) на ранніх етапах після трансплантації печінки у дітей.

**МЕТОДИ.** Проведено ретроспективне дослідження на 43 пацієнтах у віці від 0 до 18 років, які отримали трансплантацію печінки протягом 17-річного періоду. MEAF і rMELD розраховували на третій і п'ятий післяопераційний день, відповідно, та проводили регресійний аналіз (Кокс-регресія), щоб знайти кореляцію між досліджуваними показниками та смертністю в ранньому післяопераційному періоді.

**РЕЗУЛЬТАТИ.** Обидва методи оцінки виявилися статистично значущими та валідними в ранньому післяопераційному періоді після трансплантації печінки. MEAF мав значення  $p = 0,0003$  і коефіцієнт ризику 10,99, тоді як rMELD продемонстрував значення  $p = 0,003$  і коефіцієнт ризику 1,24.

**ВИСНОВКИ.** Обидві моделі MEAF та rMELD можна використовувати для діагностики ранньої дисфункції алотрансплантата та прогнозування результату трансплантації печінки у дітей, причому MEAF має діагностичну перевагу.

**КЛЮЧОВІ СЛОВА:** трансплантація печінки у дітей; рання дисфункція алотрансплантата; приживлюваність трансплантата