Prediction of Graft Dysfunction in Pediatric Liver Transplantation by Logistic Regression

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***Abstract*—Liver transplantation (LT) is the last therapeutic option for children with acute and chronic end-stage liver disease. Nowadays survival rates are over 90-95% and 70% within one year and five years post-transplantation, respectively. The main complications in the postoperative period are related to the function of the graft. The graft dysfunction early after LT is an important cause of morbidity and mortality. Numerous factors can affect the function of the graft after pediatric LT. Therefore our aim is to identify the risk factors in order to help prevent the graft failure. In the present work, by means of univariate and multivariate logistic regression analysis, the probabilities of graft dysfunction in the early postoperative period after LT are estimated. As predictors in the constructed logistic models the following parameters have been analyzed: levels of bilirubin, sodium, creatinine, international normalized ratio (INR) in blood plasma, post-transplant MELD score (Model for End-Stage Liver Disease) and cold ischemia time on the 1st, 2nd, 3rd, 5th, 7th and 10th postoperative day. The models were based on 31 patient's data obtained at the University Hospital "Lozenets" – Sofia, Bulgaria.**

Keywords: logistic regression models, liver transplantation, graft dysfunction

I. INTRODUCTION (*HEADING 1*)

Liver transplantation (LT) has received increased attention in the medical field since 1980s as a result of the introduction of new immunosuppressants and improved surgical techniques**.** LT is the treatment of choice for children with acute and chronic end-stage liver disease. Currently, the indications for LT are extended. Living donor liver transplantation in children was introduced in 1989 and by 1992 achieved a 90 % success rate. LT outcomes depend on donor factors, the preoperative condition of the recipient, surgical techniques, postoperative complications [1].

During the operation and in the postoperative period, the liver is subjected to a wide variety of potentially damaging factors. Obtaining high-quality grafts is vital to ensuring successful post transplantation outcomes [2].

Graft dysfunction is poor liver function can lead to death of the patient or re-transplantation during the postoperative days. It is a serious situation in the post-transplant setting and characterized by elevated hepatic enzymes, difficulties in elimination of bile, and coagulopathy. The exact reason for this condition is often unclear, but it is important to predict the outcome [3].

To determine whether a relationship exists between some quantitative variables representing stage of the recipient and graft dysfunction is an important purpose of research in the medicine. The objective of this study was to identify and to analyze statistically significant factors predictive of graft dysfunction in the early period of pediatric liver LT using logistic regression.

II. MATERIALS AND METHODS

For the purpose of our study, 31 children after LT were examined. The age of the children is between 1 month and 16 years, with 63% of them are under 1 year of age. The gender distribution is 60% female and 40% male. In a larger percentage (85%), transplants are from a living donor.
Donor-related factors, such as cold ischemia time (CIT) during procurement, as well as recipient-related factors, such as recipient status can affect the graft function after LT. Because of the possibility of predicting the likelihood of complication, we prefer to use the logistic regression model. As predictors (risk factors) for the graft dysfunction in the constructed logistic models there were taken blood plasma levels of bilirubin (μmol/L), sodium (mEq/L), creatinine (μmol/L), international normalized ratio (INR) of prothrombin time of blood coagulation and post-transplant Model for End-Stage Liver Disease (pMELD) on 1st, 2nd, 3rd, 5th, 7th and 10th postoperative day. The MELD score, which yields a numeric value based on serum creatinine, bilirubin and INR, has been successfully used in predicting 90-day mortality rate for patients in waiting list for LT, and has proven to be a reliable method for liver allocation. However, a careful look at the parameters of the MELD score reveals the limitations and resultant caution that should be given to ostensibly objective data [3]. Other predictors are factors warm and cold ischemia time (minutes). CIT has been widely regarded as a donor-related risk factor and it is defined as the time from cross-clamping of the donor liver to removal of the organ from cold storage solution [5].

The models were based on patient's data at the University Hospital "Lozenets" – Sofia, Bulgaria. The software package used for the statistical modeling of real data was STATISTICA 13 [6].

A. Dichotomous regression model

In this subsection we describe dichotomous regression model used for prognostic purposes [7]. The model describes the dependence of the phenomenon presence/absence of a certain complication (including disease) as a function of various factors which are accepted as independent continuous variables. The response, or the dependent binary variable y, takes two values: $y=1$ when the complication is absent and $y=0$ when the complication occurs. In the univariate logistic analysis it is supposed that the probability

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of appearance of a complication depends on the values of an affine function of the factor

$$d(x,B_0,B_1)= B_0+B_1x.$$

Here x is the factor, or descriptive variable, and B_0, B_1 are coefficients which are to be estimated by the experimental data for x and for the complications. Usually n observations for the factor x are known (in our case n=31 is the number of patients). For each complication a separate dependence on each factor is considered. Using the method of maximum likelihood estimation [7] estimates b_0 and b_1 for B_0 and B_1 are obtained. If the response y does not depend (or depends very weakly) on x then $B_1=0$.

In the multivariate logistic analysis it is supposed that the probability of appearance of a complication depends on an affine function of a vector argument with N components, namely $d(X,B)$, where

$$X=(x_1, x_2,...,x_N),\ B= (B_0, B_1,...,B_N).$$

The elements of X are factors, or independent explanatory variables, which are to be determined by the experimental data. As in the univariate analysis, there are n observations for any component of X. The influence of all factors is taken into account simultaneously. If the output y does not depend (or depends very weakly) of a certain factor x_K (k=1,2,...,N) then the corresponding coefficient B_K is zero. As a result of the statistical analysing using the likelihood method estimates $b_0, b_1,..., b_N$ for the coefficients $B_0,B_1,...,B_N$ are obtained. In the dichotomous regression model used in this paper it is supposed that

$$P(X,B)=\exp(d(X,B))/(1+\exp(d(X,B))),$$

where $\exp(.)$ is the exponential function.

The probability function $P(X,B)$ is a logistic function of the vector X for any fixed parameter B. In particular for $N=1$ the points $(X_1,P(X_1,B))$ form a logistic curve, while for $N=2$ the points $(X_1,X_2,P(X_1,X_2,P(X_1,X_2,B))$ compose a logarithmic surface. For $N>2$ the corresponding set of points is a N-dimensional variety. The Newton-Raphson iterative procedure is usually used to obtain a likelihood estimation for the coefficients $B_0,B_1,...,B_N$.

The odds of a dichotomous response is given by

$$\text{odds}=P(d(X,B))/(1+P(d(X,B))).$$

The logit transformation gives an important advantage of the model, because it is a linear function of the explanatory variables:

$$\text{Log odds}=d=B_0+B_1X_1+...+B_NX_N.$$

In comparison to the multiple linear regression model, the coefficient vector $b = (b_0,b_1,...,b_N)$ must be interpreted differently:

- The coefficients $b_1,...,b_N$ were interpreted as estimates of Log odds.
- A marginal one unit increase in X_K causes an increase in d (i.e. in Log odds) of the amount of b_K $(K=1,..., N)$.
- The confidence intervals were calculated for the odds estimates by taking the exponent of upper and lower endpoints of the asymptotic confidence interval for the Log odds.

Testing of hypothesis concerning the regression parameters can include test of a single parameter, test involving several parameters from the same regression, and joint tests involving parameters from different regressions. In multivariate logistic regression, tests for contribution of one or more parameters from the same regression are usually constructed with a large sample Wald test, with test statistics approximately distributed as a chi-square with N degrees of freedom. Values $p < 0.05$ of Wald test statistics were adopted for statistically significant.

In univariate analysis (if response depends on x) an important characteristic is the value of the factor x for which the probability is ½ (the median of the factor x) which is given by $x^* = -b_0/b_1$. This value corresponds to an inflection point of the probability curve.

III. Result and Discussion

We reviewed an unselected cohort of 31 patients (mean age 3.6 years). For the graft dysfunction in the constructed logistic models as predictors (risk factors) were taken blood plasma levels of bilirubin, sodium, creatinine, INR, and pMELD on 1st, 2nd, 3rd, 5th, 7th and 10th postoperative day. Other predictors are factors warm and cold ischemia time. At first univariate logistic models were constructed. Explanatory variables that were statistically significant in univariate analysis were included in the multivariate analysis. Using Wald's test for univariate analysis 5 statistically significant predictors were identified: INR 1st day (p = 0.039), INR 5th day (p = 0.039), pMELD 5th day (p = 0.019) and pMELD 10th day (p = 0.017) and cold ischemia (p = 0.048). The estimated logistic function for INR 1st postoperative day is given in Fig.1. The corresponding estimated logistic regression model (probability function) using software package [6] is given on the top of the figure.

The estimated negative model parameter b_1 = -1.4105 for INR 1st postoperative day indicates that the higher levels of this ratio the lower probability for the absent of graft dysfunction. As it is seen from Fig. 1 if INR1st = 4 the probability for absence of dysfunction is 0.25. The critical abscissa corresponding to probability ½ is x^* = 4.5462/1.4105 = 3.223. The estimated logistic function for INR 5th postoperative day is given in Fig. 2.

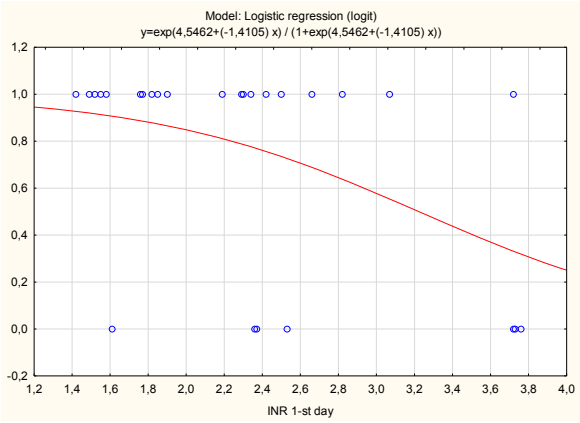

Fig. 1 The estimated probability function (red line) for absence of the graft dysfunction using levels (blue points) of the factor international normalized ratio of prothrombin time of blood coagulation after 1st postoperative day.

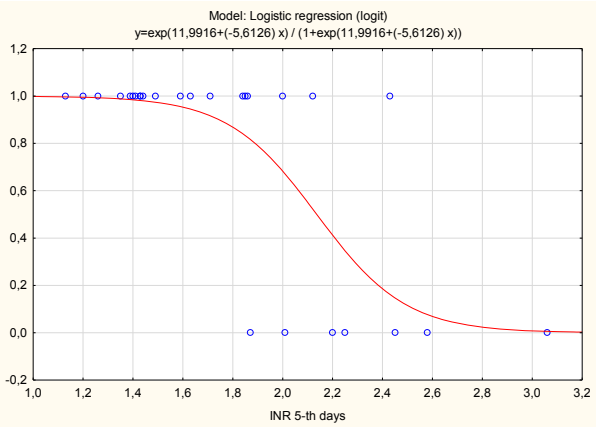

Fig. 2 The estimated probability function (red line) for absence of graft dysfunction using levels (blue points) of the factor international normalized ratio of prothrombin time of blood coagulation after 5th postoperative day.

The estimated parameter b_1 = -5.6126 is negative again and the critical point now is x^* = 11.9916/5.6126 = 2.13. The critical point corresponds to probability ½ for the graft dysfunction. The estimated logistic function for pMELD 5th postoperative day is given in Fig. 3.

The estimated negative model parameter $b1$ = -0.4105 for model coefficient for end-stage liver disease indicated that higer levels of this factor the lower probability for the absence of graft dysfunction. Similar is the shape of the probability function for pMELD 10th postoperative day with b_1 = -0.2623 (see Fig. 4.). The critical point for pMELD 5th postoperative day is x^*=6.428/0.4105=15.66, while for pMELD 10th postoperative day the corresponding value is x^*= 5.8244/0.2623 = 22.205. The critical values x^* correspond to probability 0.5 probability for graft dysfunction. Liver transplant recipients with MELD score ≥ 30 are a specific subgroup of patients with an individual high- risk profile and they need close monitoring.

The fifth significant predictor outstanding by univariate logistic analysis of data is CIT – a factor that interferes with the incidence of graft dysfunction. The cutoff for CIT is reported that a CIT > 13 hours is associated with poor outcomes after LT [4]. The estimated logistic function for INR 5th postoperative day is given in Fig. 5.

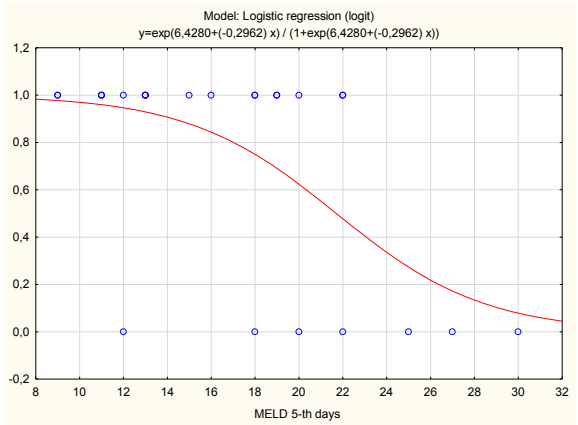

Fig. 3 The estimated probability function (red line) for absence of graft dysfunction using levels (blue points) of the factor model coefficient for end-stage liver disease after 5th postoperative days.

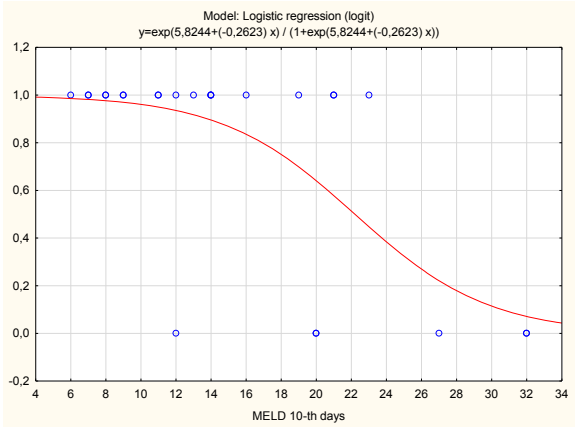

Fig. 4 The estimated probability function (red line) for absence of graft dysfunction using levels (blue points) of the factor model coefficient for end-stage liver disease after 10th postoperative days.

The estimated parameter $b1$= - 0.0058 for CIT is negative and the critical point now is x^*=3.0626/0.0058=528 minutes (8.8 hours). Using this model we predict the probability for CIT = 780 minute (13 hours):

$$P = \exp(3.0626 - 0.0058*780)/(1 +$$

$$+ \exp(3.0626 - 0.0058*780)) = 0.1883.$$

The prediction is that the probability for CIT is 0.1883, i.e. the chance for the absence of graft dysfunction is only about 19%. This result agrees with other findings in medical literature [1-4].

Statistically significant factors, received with univariate analysis, are taken as exploratory variables for multivariate logistic regression analysis. Estimated parameters, its p-levels and the corresponding odds ratios are presented in Table I.

Pediatric liver transplantation is one of the most up-to-date and fast-growing areas in contemporary medicine. The purpose of LT is not only to ensure the patient survival but also to offer him/her a state of health which enables him/her to achieve psychological and physical integrity. The fact requires accurate prediction of complications after LT, in particular graft dysfunction.

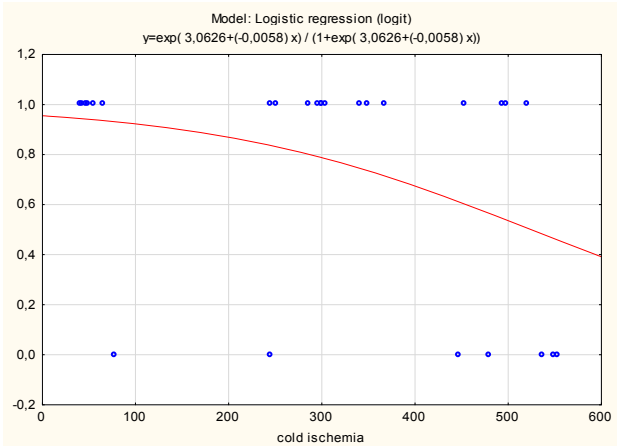

Fig. 5 The estimated probability function (red line) for absence of graft dysfunction using levels (blue points) of the factor cold ischemia.

TABLE I. ESTIMATED PARAMETERS OF MULTIVARIATE LOGISTIC REGRESSION

n=31	Model: Logistic regression (logit) Dependent variable: graft dysfunction loss: max likelihood Final loss: 2.878, $Chi^2(5)=21.798$, p=0.00057 Modeled probability that graft dysfunction is absent					
	B0 (p-level)	B1 cold ischemia (p-level)	B2 pMELD 5th day (p-level)	B3 pMELD 10th day (p-level)	B4 INR 1st day (p-level)	B5 INR 5th day (p-level)
Estimates	59.53 (0.03)	-0.002 (0.046)	-0.849 (0.003)	-0.669 (0.012)	-4.88 (0.045)	-20.285 (0.003)
Odds ratio		0.9970	0.4274	0.5119	131.90	0.0001

Obtaining high-quality prediction models for donor and recipient related risk factors is a condition to ensuring successful post transplantation outcomes.

In our future research we intend to look for the relationship between plasma level of vitamin D and graft dysfunction. The first step in the activation of vitamin D takes place in the liver, therefore its synthesis is closely related to the hepatic function. However, the plasma level reguared for the immune modulating action of vitamin D remain unknown [8]. We hope the plasma level of vitamin D could be a predictor of graft dysfunction after pediatric liver transplantation.

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