Validity Of Clinical Parameters In Prediction Of Outcome For Orthotopic Liver Transplant

I Zemek, K Sofi, M Abolfotouh

Citation

I Zemek, K Sofi, M Abolfotouh. *Validity Of Clinical Parameters In Prediction Of Outcome For Orthotopic Liver Transplant*. The Internet Journal of Anesthesiology. 2012 Volume 30 Number 3.

Abstract

Background: There have been many controversies with regard to the validity of different clinical parameters in the prediction of Orthotopic Liver Transplant (OLTx) outcome. Aim: The aim was to test the validity of different clinical parameters in the prediction of the outcome of Orthotopic Liver Transplant (OLTx) at King Abdulaziz Medical City, Riyadh, Saudi Arabia. Methods: A retrospective study of the different clinical parameters of 25 cases of End Stage Liver Disease (18 males and 7 females) ages from 11 to 70 years was done. These parameters were: operative duration (incision to skin closure time), highest and lowest Heart rate and Mean arterial pressure during the procedure, estimated blood lost, lowest Oxygen saturation. Biophysical outcomes were collected: lowest Platelets and Fibrinogen, highest Lactic acid, INR and Creatinine, Age of the patient and Warm ischemia time. The outcome in terms of major complications and / or death was correlated with these parameters. Receiver operating characteristic curve was applied to identify the validity of each parameter. Results: Highest INR was only parameter significantly associated with outcome of OLTx within 30 days (p = 0.044, c-index = 0.78). The value of 3.4 was the optimum cut off point giving the best validity for prediction of outcome" with 67% of sensitivity and 88% specificity " Conclusion: INR is the only predictor associated with major complication or death within 30 days post OLTx at cut of level of > 3.4

INTRODUCTION

Liver disease is a major health problem in Kingdom of Saudi Arabia with Hepatitis B accounting for 49.3% and Hepatitis C about 40.7%.Approximately 20% of Hepatitis C infected individuals progress to end stage liver disease. [1] Tranplantation has become the standard for end-stage liver disease over the past three decades. [2] Organ Transplant Programs have been successful since early 1990s in the Kingdom of Saudi Arabia. [3,4] Although Liver Transplantation has changed the outcome of patients with end-stage liver disease (ESLD), the limited availability of organ in the face of large demand leads to long waiting lists. [5] The need for a suitable method of prediction of mortality from end-stage liver disease from the perspective of liver transplantation has been emphasized, so the patient likely to live shorter gets the organ earlier than a patient who would live longer. [6] Several scoring systems have been described to evaluate prognosis of patients with ESLD and also to predict outcome after liver transplant. [7, 8,9,10] However most of these are complex with limited predictive ability. Recently the Model for End-Stage Liver Disease (MELD) score has been adapted to measure disease severity, outcome, and as a basis of determination of organ allocation policies. [11] Although popular, it is not free from flaws. MELD score is calculated using serum bilirubin, creatinine and international normalized ratio (INR).The limitations of these prognostic scoring systems have led to search for other predictive indices. [12]

This retrospective cohort study was conducted in King Fahd National Guard Hospital, Riyadh, Saudi Arabia. The Liver Transplant Programme started in 1994 in this hospital and since that time till 2008 257 cases of Orthotopic liver transplant from Cadaver donors were done and only 50 patients could be traced. The purpose of this study was to test the validity of different clinical parameters in the prediction of outcome of Orthotopic Liver Transplant at King Fahd National Guard Hospital, Riyadh, Saudi Arabia.

METHODS

We collected perioperative data in Liver Transplant patients from Medical Records Department, after approval of the Institutional Review Board at King Fahd National Guard Hospital, Riyadh, Saudi Arabia. Files of 50 patients could be traced and only 25 files revealed complete data and were included in the study

Recipients intra-operative variables: Duration of surgery, heart rate and mean arterial pressure(highest and lowest values),oxygen saturation(lowest values),warm ischemia time, estimated blood loss, platelet and fibrinogen levels,INR,creatinine and lactic acid levels, were recorded. The age and associated co-morbidities were also considered. Patients with malignancies were excluded.

Primary outcome of this study was death and major complication within 30 days after the surgery. The following events were defined as major complications: Acute renal failure, acute graft rejection, re-exploration due to leak of artery/bile duct system, cardiac arrest requiring CPR, pulmonary embolism, stroke, pneumonia and sepsis. Patients having complications categorized in the database as "other occurrence "were reviewed individually to determine the severity of complication.

STATISTICAL ANALYSIS

All analyses were performed using SPSS software program version 17.0. Mann–Whitney test and Fisher Exact test were applied as appropriate, Variables that were significantly associated with major complication or death, in the bivariate analyses, became our candidates for applying the receiver operating characteristic (ROC) curve, striving for the predictive power. For all patients, all values of the different parameters, including the duration of operation and age, were cross classified according to their outcome status (no or minor complications & death or major complications), and by various cut-off points along the range of each parameter, above which patients may die or have major complications. From these tabulations, the sensitivity, specificity and predictive values were computed for each parameter at each cut-off point.

RESULTS

We reviewed 50 patients of which only 25 (18 males and 7 females) ages from 11 to 70 years, had sufficient data in anesthesia records and file to enter this study. Major complications occurred within 30 days in 7 of these 25 cases (28 %) including 3 deaths (12 %).

Table 1 shows the perioperative mean± SD for the different clinical parameters according to the outcome of OLTx, in terms of no or minor complications and death or major complications. Of all these parameters, only the INR showed significantly different mean between patients whose outcome was good and those whose outcome was bad.(z=1.99, p=0.044).

Table 2 is a cross – tabulation of the 23 patients according to their outcome and the cutoff point of 3.4 or more for INR. At this particular cut off level, it is noted that the sensitivity of this parameter was 0.67, specificity was 0.88 and false positive rate (1-specificity) was 0.12. On the other hand, 2/23 (8, 7%) of patient were misclassified as having favorable outcome.

Figure 1

Table 1. Mean (± SD) of Perioperative clinical parameters by outcome of OLTx in 25 patients at King Abdulaziz Medical City, Riyadh, Saudi Arabia

Parameter	Non -Complicated $\bar{x}$± SD	Complicated $\bar{x}$ ± SD	Z value	P value
EBL (ml)	2305±2509	2485±3376	0.092	0.929
Lowest MAP (mm Hg)	51.17±6.57	52.43±10.92	0.152	0.883
Lowest HR(beats / min)	60.8±19.0	53.7±17.4	1.214	0.244
Warm ischemia time (min)	52.6±13.8	58.3±27.9	0.633	0.591
Highest INR	2.83±1.71	4.85±2.78	1.999	0.044*
Lowest Platelets(thous)	63.6±30.9	52.0±33,8	1.302	0.198
Lowest Fibrinogen	0.84±0.41	1.18±0,44	1.916	0.055
Surgical Time(hrs)	7.82±2.64	9.02±3.36	0.999	0.326
Highest Lactic acid(mmol/L)	4.51±2.32	5.62±4.21	0.210	0.865
Age(yr)	48.33±17.45	46.14±16.82	0.454	0.657
Creatinine(mmol/L)	82.77±33.69	198.71±243.28	0.303	0.865
Diabetes (No %)	8 (44.4%)	4 (57.14%)		0.673ª
Sex (M/F ratio)	13/5	5/2		0.663ª

* Statistically significant
ª Fisher's exact test was applied

Figure 2

Table 2. 2 x 2 Classification of 23 patients by the cutoff point of ≥ 3.4 INR and outcome of OLTx at King Abdulaziz Medical City, Riyadh, Saudi Arabia

INR	Outcome		Total
	Death/major complications	No/minor complications	
3.4 or more	4	2	6
< 3.4	2	15	17
Total	6	17	23

Fisher's Exact test, p.value= 0.021
Sensitivity 4/6 = 66.6 %
Specificity 15/17 = 88.2 %
Positive Predictive value: 4/6 = 66.6 %
Negative Predictive value: 15/17 = 88. %
False positive rate = 1-specificity = 1-0.88 = 0.12

DISCUSSION

The misclassification of the patients who undergo Orthotopic Liver Transplantation (OLTx) in terms of outcome based on the values of different laboratory parameters tends to result in false reassurance, and/ or false

warnings. However, the misclassification in the present study was in favor of false reassurance rather than reassurance, with 12% of patients misclassified as favorable outcome.

The need for OLTx is predicted by clinical assessment based on the Model of End-stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) score. [13, 14] Whether MELD predicts survival after OLTx is controversial. [15] MELD describes hepatic and renal parameters but does not reflect mortality and morbidity influencing factors of the recipient, which are of equal relevance in determining the outcome after OLT. [16] Although large number of studies vote in favour of MELD as a reliable measure of mortality risk in patients with ESLD and suitable for use as a disease severity index to determine organ allocation priorities. [17] However the hunt for more reliable predictors of outcome continues. In one study creatinine was found as the only variable to be an independent predictor of survival. [18] Another study suggested that Age,pre OLTx creatinine and cholinesterase as predictors of short term post OLT survival and may be helpful as a bedside score in pre OLTx clinical management, outcome prediction and decision making. [19] In a pediatric liver transplant study, it was mentioned that the prognostic criteria for mortality in pediatrics are less well defined compared to the adult population, although significantly elevated INR of 4 and above carries a high chance of death and liver transplantation should be considered at this stage. [20] All scoring systems used in clinical practice related to OLT have not shown any scoring system as a predictor of survival during OLTx. [21]

In our study we looked into the possible correlation between various peri-operative clinical parameters and the post liver transplant survival. The relatively good level of sensitivity and specificity found in this study for the INR at cut off level of 3.4 suggest that this parameter could be potentially useful. Its sensitivity of 0.67 will result in false reassurance in 33% while its specificity of 0.88 will result in a false warning in 12%.

The study might have sources of considerable measurement variability. We took data from electronic anesthesia records which record vital signs every 3 minutes. For any given patient, there can be artifacts in automatic readings. Blood loss estimation can be similarly imprecise. Also the laboratory values are usually taken every hour, so the peak of each variable can easily be skipped.

From the collective findings of this study and taking into account its limitations and small sample size, it is considered preliminary and suggested for potential validity of advantage of highest INR at the specified cut off point.

CONCLUSION

Findings of this study highlight that only peri-operative INR greater than 3.4 is significantly associated with major complications or death within 30 days post Orthotopic liver transplantation. However further studies to confirm these findings are recommended.

References

1. Al-Tawfiq JA, Anani A. Profile of viral hepatitis A, B, and C in a Saudi Arabian hospital. Med Sci Monit. 2008 Jan; 14(1):CR52-56.
2. National Institute of Health Consensus Development Conference Statement.Liver TransplantationHepatology 1983; 4(1):1075-105.
3. Shaheen FA, Souqiyyeh MZ, Al-Swailem AR. Saudi center for organ transplantation: activities and achievements. Saudi J Kidney Dis Transpl. 1995 January-March; 6(1):41-52.
4. Al Sebayel M, Kizilisik AT, Ramirez C, Altraif I, Hammad A, Littlejohn W, de Cordier MB, Geldhof G, Bhatti TJ, Abdulla A. Liver transplantation at king fahad national guard hospital riyadh, kingdom of saudi arabia. Saudi J Kidney Dis Transpl. 1996 Apr-Jun; 7(2):173-7.
5. Blumenthal D. The future of quality measurement and management in a transforming health care system. JAMA. 1997 Nov 19; 278(19):1622-5.
6. Infante-Rivard C, Esnaola S, Villeneuve JP. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. Hepatology. 1987 Jul-Aug; 7(4):660-4.
7. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from child to MELD. Mayo End-stage Liver Disease. Hepatology. 2001 Feb; 33(2):473-5.
8. Ho YP, Chen YC, Yang C, Lien JM, Chu YY, Fang JT, Chiu CT, Chen PC, Tsai MH. Outcome prediction for critically ill cirrhotic patients: a comparison of APACHE II and Child-Pugh scoring systems. J Intensive Care Med. 2004 Mar-Apr; 19(2):105-10.
9. Nagashima I, Takada T, Okinaga K, Nagawa H. A scoring system for the assessment of the risk of mortality after partial hepatectomy in patients with chronic liver dysfunction. J Hepatobiliary Pancreat Surg. 2005; 12(1):44-8.
10. Serra MA, Puchades MJ, Rodríguez F, Escudero A, del Olmo JA, Wassel AH, Rodrigo JM. Clinical value of increased serum creatinine concentration as predictor of short-term outcome in decompensated cirrhosis. Scand J Gastroenterol. 2004 Nov; 39(11):1149-53.
11. Huo TI, Lin HC, Wu JC, Lee FY, Hou MC, Lee PC, Chang FY, Lee SD. Proposal of a modified Child-Turcotte-Pugh scoring system and comparison with the model for end-stage liver disease for outcome prediction in patients with cirrhosis. Liver Transpl. 2006 Jan; 12(1):65-71.
12. Ghoshal UC, Das A. Models for prediction of mortality from cirrhosis with special reference to artificial neural network: a critical review. Hepatol Int. 2008 Mar; 2(1):31-8.
13. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease

(MELD) and allocation of donor livers. Gastroenterology. 2003 Jan;124(1):91-6.
14. Boin IF, Leonardi MI, Pinto AO, Leme RS, Udo E, Stucchi RS, Soares EC, Leonardi LS. Liver transplant recipients mortality on the waiting list: long-term comparison to Child-Pugh classification and MELD. Transplant Proc. 2004 May; 36(4):920-2.
15. Cholongitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, Burroughs AK. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl. 2006 Jul; 12(7):1049-61.
16. Nagler E, Van Vlierberghe H, Colle I, Troisi R, de Hemptinne B. Impact of MELD on short-term and long-term outcome following liver transplantation: a European perspective. Eur J Gastroenterol Hepatol. 2005 Aug; 17(8):849-56.
17. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001 Feb; 33(2):464-70.
18. Desai NM, Mange KC, Crawford MD, Abt PL, Frank AM, Markmann JW, Velidedeoglu E, Chapman WC, Markmann JF Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function. Transplantation. 2004 Jan 15; 77(1):99-106.
19. Weismüller TJ, Prokein J, Becker T, Barg-Hock H, Klempnauer J, Manns MP, Strassburg CP. Prediction of survival after liver transplantation by pre-transplant parameters. Scand J Gastroenterol. 2008; 43(6):736-46.
20. Aw MM, Dhawan A. Acute liver failure. Indian J Pediatr. 2002 Jan; 69(1):87-91.
21. Hwang WJ, Jeon JP, Kang SH, Chung HS, Kim JY, Park CS.Sluggish decline in a post transplant model for end-stage liver disease score is a predictor of mortality in living donor liver transplantation. Korean J Anesthesiol. 2010 Sep; 59(3):160-6.

Author Information

Ivo Zemek, MD
Associate Consultant, Department of Anaesthesia, King Fahad National Guard Hospital

Khalid Sofi, MD
Assistant Consultant, Department of Anaesthesia, King Fahad National Guard Hospital

Mostafa A. Abolfotouh, MD
Head, Medical Team (Biobanking Section), King Fahad National Guard Hospital