• BASIC RESEARCH •

Multivariate regression analysis on early mortality after orthotopic liver transplantion

Ye-Ben Qian, Gui-Hua Cheng, Jie-Fu Huang

Ye-Ben Qian, Department of hepatic biliary surgery, first affiliated hospital An Hui Medical University, HeFei 230022, AnHui Province, China
Gui-Hua Cheng, Jie-Fu Huang, Organ transplantation center, first affiliated hospital, Sun Yat-Sen University of Medical Sciences, GuangZhou 510089 GuangDong Province China
Correspondence to: Dr Ye-Ben Qian, Department of hepatic biliary surgery, first affiliated hospital An Hui Medical University, HeFei 230022, AnHui Province, China. ayqianyb@163.net
Telephone: +86-551-5129029

Abstract

AIM: **To identify the risk factors relating to early mortality after orthotopic liver transplantation.**

METHODS: **Clinical data of 37 adult patients undergoing liver transplantation were retrospectively collected and divided into two groups: the survived group (survival time $\geq$30 d) and the death group (survival time<30 d). The relationship between multivariate risk factors and early mortality after orthotopic liver transplantation were analyzed by stepwise logistic regression.**

RESULTS: **The survival rate was 73%. Early mortality rate was 27%. APACAE Ⅲ, preoperative serum creatinine level and interoperative bleeding quantity had a significant independent association with early mortality. (R=0.1841, 0.2056 and 0.3738).**

CONCLUSION: **APACHE Ⅲ,preoperative serum creatinine level and interoperative bleeding quantity are significant risk factors relating to early mortality after orthotopic liver transplantation. To improve the recipient's preoperative critical condition and renal function and to reduce interoperative bleeding quantity could lower the early mortality after orthotopic liver transplantation.**

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INTRODUCTION

In recent years, the success rates of orthotopic liver transplantation (OLT) have improved markedly as a result of rapid advances in immunosuppressions, surgical and preservation techniques. One-year survival rate after liver transplantation exceeds 80%. Orthotopic liver transplantation, as an accepted treatment for end-stage liver disease, has been widely performed in the world[1-5]. In our country, the early mortality after OLT remains relatively high and current studies have focused on the improvement of survival rate after liver transplantation[6,7]. Clinical data of 37 adult patients undergoing liver transplantation were retrospectively collected in our study. The significant risk factors relating to early mortality after OLT were analyzed and determined, which may contribute to the selection of candidate and improvement of survival in patients with liver transplantation.

MATERIALS AND METHODS

Materials

Thirty-seven adult patients undergoing OLT procedures at our transplantation center from September 1993 to January 2000 were studied. The study population consisted of 32 men and 5 women with a mean age of 39.8(range 17-64) years. The grafts were obtained from donors. Indications for liver transplantation were end-stage liver cirrhosis (n=9), fulminant hepatic failure (n=8), primary liver cancer (n=14), primary sclerosing cholangitis (n=2), Willson's disease (n=1), polycystic liver and kidney (n=1), hepatoangioma (n=1), and cholangiocarcinoma (n=1).

Multiple risk factors

Thirty-seven patients were divided into two groups: survival group (survival time $\geq$30 d) and death group (Survival time <30 d).There were different possible risk factors relating to early mortality after liver transplantation including preoperative, interoperative and postoperative ones. Preoperative information consisted of age, APACHEⅢ hepatoencephalopathy, previous abdominal surgery, serum albumin, prothrombin time (PT),serum creatinine level (Cr),serum Aspartate transaminase (AST),white blood cells counts (WBC),platelet counts(PLC) and dismatch ABO group. Interoperative information included heat ischemic time, cold ischemic time, anhepatic time and bleeding quantity. Postoperative information included of rate of acute rejection and postoperative complications rate (including biliary leakage, cytomegalovirus(CMV)infection, hepatic artery thrombosis, hydrothorax and myocardiac infarction, etc).

Statistical methods

Experimental data were presented as $x \pm s$ and frequency. For continuous data, independent 2-tailed t tests were used to determine whether there were significant differences between the two groups. Pearson's Chi-square statistics were used to test differences in all frequencies. Data with significant difference were entered into a stepwise logistic regression analysis. And all of the statistical calculations were performed using the SPSS (version: 9.0, Chicago,USA).

RESULTS

Twenty-seven of the 37 adult patients survived more than one months after liver transplantation. Early survival rate was 73% while early mortality was 27%. The other 10 patients died postoperatively within 30 d and the major cause for their death were disseminated intravascular coagulation (DIC n=2), myocardial infarction (n= 2), acute renal failure (n=2), hepatic artery thrombosis (n=1), cerebral bleeding (n=1) and adult respiratory distress syndrome (ARDS)(n=1).

Comparison between the survival group and the death group showed significant differences only in terms of age, APACHE Ⅲ, serum creatinine level, PT, was PLC and interoperative bleeding quantity, (P<0.05, Table 1). The stepwise logistic regression were used to create the best statistical model relating to early mortality after transplantation. The factors that had significant independent

associations with early mortality after the stepwise procedure were APACHE Ⅲ, serum creatinine level and interoperative bleeding quantity, with regression coefficients of 0.1841, 0.2056 and 0.3738, respectively (Table 2).

Table 1 Risk factors relating to early mortality after liver transplantation

Risk factors	Survival group (n=27)	Death group (n=10)	P value
Age(yrs)	38.3±2.5	47.8±2.2	0.0000
Previous abdominal surgery	11% (3/27)	30% (3/10)	0.3130
APACHE Ⅲ (score)	40.5±6.7	63.4±12.9	0.0000
Hepatoencephalopathy	15% (4/27)	40% (4/10)	0.1712
Serum creatinine level (μmol·L⁻¹)	82.2±10.8	132.8±33.2	0.0000
AST (nkat·L⁻¹)	97.9±18.6	125.8±80.5	0.0951
Albumin (g·L⁻¹)	36.9±1.7	32.7±2.9	0.0000
TB (imol·L⁻¹)	298.3±67.9	314.9±87.1	0.5447
PT /s	22.5±3.2	25.5±3.7	0.0175
WBC/ (×10⁹·l⁻¹)	7.3±1.2	6.8±1.1	0.2351
PLC /(×10⁹·l⁻¹)	129.5±17.5	53.4±12.3	0.0000
Dismatich ABO group	7.3% (2/27)	30% (3/10)	0.1102
Heat ischemic time /min	3.8±0.1	3.9±0.3	0.1478
Cold ischemic time /s	464.9±26.9	471.2±46.3	0.6104
Anhepatic time/s	87.5±4.9	90.3±10.5	0.2704
Interoperative bleeding quantity /ml	5615.1±1003.7	12263.6±3606.1	0.0000
Rate of acute rejection	18% (5/27)	20% (2/10)	1.0000
Rate of postoperative complications	59% (16/27)	70% (7/10)	0.709

Table 2 Stepwise logistic regression analysis

Variable	B	SE	Wald	df	Sig	R
APACHE Ⅲ	0.340	0.0141	5.8481	1	0.0156	0.1841
Serum creatinine level (Cr)	3.6542	1.4013	6.8002	1	0.0091	0.2056
Interoperative bleeding quantity	2.0194	0.7516	7.2182	1	0.0020	0.3738

DISCUSSION

Orthotopic liver transplantation is a treatment for end-stage liver disease. Early mortality was below 10%[8,9], which remains high in our country. The serious preoperative condition of recipient and the late timing for operation may account for this result[10,11]. A number of investgators have examined the factors associated with outcome after liver transplantation including PT, APACHE Ⅲ and so on[12-16]. In our study, 10 of 37 patients died postoperatvely, with an early mortality of 27%. After analyzed with stepwise logistic regression, APACHE Ⅲ、 preoperative serum creatinine level (Cr) and interoperative bleeding quantity showed significant associations with early mortality after liver transplantation.

While APACHE Ⅲ score is a best predictor of mortality[17,18,19], APACHE Ⅲ that results from the addition of 3 groups of variables (acute physiology, age and chronic health) consists of multiple organ function evolution, including heart, lung, liver, kidney, brain, etc. It is more accurate than APACHE Ⅲ. And now it has been widely used to evaluate the severely illed in patients' condition and to predict the mortality of patients[20,21]. In our study, the APACHE Ⅲ score was 40.5±6.7 and 63.4±12.9 in the survival group and the death group respectively. There was a statistical difference between the two groups in APACHE Ⅲ score,*P*<0.001. The stepwise logistic regression analysis showed a significant independent association with early mortality after transplantation, with a regression coefficient of 0.1841. As one of the main risk factors, it can act as a reference index of the selection of recipient and timing for operation.However because it is not specific to liver function, it needs combination with other indexs when used to predict outcome of OLT.

Renal dysfunction is a common dangerous complication in patients with end-stage liver disease. It results from acute tubular necrosis and caused by hepatorenal syndrome[22-25]. Gunning[26] reported a significant decrease of 43% in glomerular filtration rate (GFR) during transplantation in patients with normal renal function. Both high preoperative serum creatinine level and interoperative venovenous bypass can lead to renal hemodynamic unstablity during operation[27,28,29]. The postoperative nephrotoxic immunosuppressions can also contribute to the irreversible renal insufficiency, leading to renal failure after liver transplantation[30,31]. In our study, 2 of 10

patientsdied of renal failure, who were all along with high preoprative serum creatinine level and hepatorenal syndrome before transplantation. A significant differencewas found between the survival group and the death group was shown in serum creatinine level (*P*<0.001), with a mean of 82±11 and 133±33, respectively. The stepwise logistic regression analysis, it also showed a statistical independent association with early mortality after liver transplantation, with a regression coefficient of 0.2056. It is also a main risk factor which predicts early mortality after OLT. It is very important to correct renal malfunction before transplantation. How to prevent and treat renal failure Kuse[32] reported that Urodilatin can treat acute renal failure following OLT. Gonwa and the other investgators[33-36] reported that renal failure need dialysis. Our principles were to avoid using nephrotoxic treatments and drugs, to maintain stable hemodynamically and monitor central venous pressure,to use small dose of Dopamine (2-5μg·kg⁻¹min⁻¹) and Procaine to dilate renal artery and protect renal function,to use diuretics appropriately, to perform hemodialysis properly performed if needed, and not to use Alprostadil(PGE1).[37]

Interoperative bleeding quantity is the third important risk factor relating to early mortality after liver transplantation[38]. If it exceeded 10000ml, mortality was very high. The interoperative bleeding quantity of the death group was more than that of the survival group statistically (*P*<0.05), with a mean of 12264±3606mL and 5615±1004mL respectively. Logistic regression analysis showed a significant relationship between interoperative bleeding quantity and early mortality after transplantation, with a regression coefficient of 0.3738. Severe bleeding and a large amount of transfusion during operation may lead to hemodynamic unstablity and DIC. And long-term hypopiesia may accelerate preoperative renal insufficiency, leading to irreversible renal failure,and increasing the early mortality after operation[39,40]. Interoperative severe bleeding may due to previous upper abdominal surgery, abdominal extensive adhesions, portal hypertension, splenic hyperfunction, severe coagulation disorders,etc.[41-44] In our study, there was no significant difference between the two groups with previous surgical histories. But it should be emphasized that some of our findings might be accidental because of insufficient cases involved in the study. We should pay attention to these patients with previous surgical histories. In these patients, severe bleeding and coagulation disorders may occur during operation because of abdominal extensive adhesions and difficulties in sequestration and ligation, consequently DIC and acute renal failure may follow. In our centre, 2 patients developed DIC.

The other risk factors showed no significant associations with early mortality after liver transplantation. But some of the factors did influence the outcome of the recipients and should be considered carefully, including dismatch ABO group,heat ischemic time, cold ischemic time, rate of acute rejection, rate of postoperative complications., etc[45-51]. Except emergent cases, the recipients and the donors were matched in ABO group at our center. Heat ischemic time and cold ischemic time were also limited strictly within 5 min and 12 h respectively during operation. After transplantation, ultrasonography B, chest X-ray examination,CMV detection and liver biopsy were performed periodically. Acute rejection and other postoperative complications were diagnosed and treated earlier. In patients diagnosed as having acute rejection,a large dose of methylprednisolone and FK506 were administrated with a treatment rate of 100%. Therefore, these risk factors showed no significant value in statistical analysis in our study.

REFERENCES

1   Starzl TE, Demetris AJ. Liver transplantation: a 31-year perspective. *Curr Probl Surg* 1990; 27:55-106

2   Bismuth H, Farges O, Castaing D, Samuel D, Adam R, Johann M, Azoulay D, Feray C, Astarcioglu I,Saliba F.Evaluation of results of liver transplantation: Experience based on a series of 1052 transplantation. *Presse Med* 1995; 24:1106-1110

3   Parrilla P, Sanchez-Bueno F, Figueras J, Jaurrieta E, Mir J, Margarit C, Lazaro J, Herrera L, Gomez-Fleitas M, Varo E, Vicente E, Robles R, Ramirez P. Analysis of the complications of the piggy-back technique in 1,112 liver transplants. *Transplantation* 1999; 67: 1214-1217

4   Ryckman FC, Alonso MH, Bucuvalas JC, Balistreri WF. Long-term survival after liver transplantation. *J Pediatr Surg* 1999; 34: 849-850

5   Goss JA, Schakleton C, Farmer D, Amout W, Seu P, Markowitz J, Martin P. Orthotopic liver transplantation for primary sclerosing cholangitis-a 12 year, single-center experience. *Ann Surg* 1997; 225: 472-481

6   Xia SuiSheng. Current status of liver transplantation in China. *Shijie Huaren Xiaohua Zazhi* 1999;7:645-646

7   Huang Jiefu. Organ transplantation in china: current status and strategy. *ZhongHua Waike ZaZhi* 1999; 37:535-537

8   Doyle HR, Marino IR, Jabbour N,Zetti G, McMichael J, Mitchell S, Fung J, Starzl TE. Early death or retransplantation in adults after orthotopic liver transplantation. *Transplantation* 1994; 57:1028-1036

9   Deschenes M, Belle SH, Krom RA, Zetterman RK, Lake JR. Early allograft dysfunction after liver transplantation. *Transplantation* 1998; 66: 302-310

10   Chung SW, Kirkpatrick AW, Kim HL, Scudamore CH, Yoshida EM. Correlation between physiological assessment and outcome after liver transplantation. *Am J Surg* 2000; 179: 396-399

11   Spanier TB, Klein RD, Nasraway SA, Rand WM, Rohrer RJ, Freeman RB, Schwaitzberg SD. Multiple organ failure after liver transplantation. *Crit Care Med* 1995; 23: 466-473

12   Baliga P, Merion RM, Turcotte JG, Ham JM, Henley KS, Lucey MR, Schork A, Yushyr MS, Campbell DA Preoperative risk factor assessment in liver transplantation. *Surgery* 1992; 112:704-711

13   Cillo U, Tedeschi U, Carraro P, Burra P, Varagnolo M, Ambrosino G, Cionfoli M, Brolese A,Borin L, Zanus G. Early predictive markers of irreversible graft dysfunction After liver transplantation. *Transplant Proc* 1994; 26: 3599-3601

14   Bein T, Frhlich D, Pmsl J, Forst H, Pratschke E. The predictive value of four scoring systems in liver transplant recipients. *Intensive Care Med* 1995; 21: 32-37

15   Clavien PA, Camargo CA, Croxford R, Langer B, Levy GA, Greig PD. Definition and classification of negative outcomes in solid organ transplantation. Application in liver transplantation. *Ann Surg* 1994; 220: 109-120

16   Ricci P, Therneau TM, Malinchoc M, Benson JT, Petz JL, Klintmalm GB, Crippin JS. A prognostic Model for the outcome of liver transplantation in patients with cholestatic liver disease. *Hepatology* 1997; 25: 672-677

17   Angus DC, Clermont G, Kramer DJ, Linde-Zwirble WT, Pinsky MR. Short-term and long-term outcome prediction with the Acute Physiology and Chronic Health Evaluation II system after orthotopic liver transplantation. *Crit Care Med* 2000; 28:150-156

18   Sawyer RG, Durbin CG, Rosenlof LK, Pruett TL. Comparison of APACHE II scoring in liver and kidney transplant recipients versus trauma and general surgical patients in a single intensive-care unit. *Clin Transplant* 1995;9:401-405

19   Bein T, Forst H, Pratschke E. Apache-II-scoring in the liver transplant recipient. *Intensive Care Med* 1992; 18:60-61

20   Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy D, Tedlotring MS, Damiano A MS, Harrell. The APACHE Ⅰⅰⅰ prognostic system risk prediction of hospital mortality for critically hospitalized adults. *Chest* 1991; 100:1619-1636

21   Bernal W, Wendon J, Rela M, Heaton N, Williams R. Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. *Hepatology* 1998; 27:1050-1055

22   Fraley DS, Burr R, Bernardini J, Angus D, Kramer DJ, Johnson JP. Impact of acute renal failure on mortality in end-stage liver disease with or without transplantation. *Kidney Int* 1998; 54:518-522

23   Alvares-da-Silva MR, Waechter FL, Franciscni CF, Barros E, Thome F, Traiber C, Fonseca DL, Zingani JM,Sampaio JA, Pinto RD, Pereira-Lima L. Risk factors for postoperative acute renal failure at a new orthotopicliver transplantation program. *Transplant Proc* 1999; 31: 3050-3052

24   Palapattu GS, Barbaric Z, Rajfer J.Acute bilateral renal cortical necrosis as a cause of postoperative renal failure. *Urology* 2001; 58:281

25   Kes P. Hepatorenal syndrome: new perspectives in pathophysiology and management. *Acta Med Croatica* 2000; 54:165-173

26   Gunning TC, Brown MR, Swygert TH, *et al.* Perioperative renal function in patients undergoing orthotopic liver transplantation. *Transplantation* 1991; 51: 422-427

27   Lafayette RA, Paré G, Schmid CH, King AJ, Rohrer RJ, Nasraway SA. Pretransplant renal dysfunction predicts poorer outcome in liver transplantation. *Clin Nephrol* 1997; 48:159-164

28   Thomas G, Kelly D, Norris S, Crosby O, Hegarty J, Crowley K, McEntee G, Traynor O, Watson A, Keogh B Acute renal failure in orthotopic liver transplantation. *Ir J Med Sci* 1996; 165:271-273

29   Pascual E, Gomez-Arnau J, Pensado A, de la Quintana B, Carrera A, Arribas MJ, Garcia-Guiral M, Cuervas- Mons V. Incidence and risk factors of early acute renal failure in liver transplant patients. *Transplant Proc* 1993; 25:1837

30   Platz KP, Mueller AR, Blumhardt G, Bachmann S, Bechstein WO, Kahl A, Neuhaus P. Nephrotoxicity following orthotopic liver transplantation. A comparison between cyclosporine and FK506. *Transplantation* 1994; 58:170-178

31   Van Buren D, Payne J, Geevarghese S, MacDonell R, Chapman W, Wright JK, Helderman JH, Richie R, Pinson CW. Renal function in primary liver transplant recipients receiving neoral (cyclosporine) versus prograf (tacrolimus). *Transplant Proc* 1998; 30:1401-1402

32   Kuse ER, Meyer M, Constantin R, Oldhafer K, Schlitt HJ, Schulz-Knappe P, Uberbacher HJ, Pichlmayr R, Forssmann WG. Urodilatin (INN: ularitide). A new peptide in the treatment of acute kidney failure following liver transplantation. *Anaesthesist* 1996; 45:351-358

33   Gonwa TA, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, Klintmalm GB.Renal replacement therapy and orthotopic liver transplantation: the role of continuous veno-venous hemodialysis. *Transplantation* 2001; 71:1424-1428

34   L¨ⁱtkes P, Lutz J, Loock J, Daul A, Broelsch C, Philipp T, Heemann U. Continuous venovenous hemodialysis treatment in critically ill patients after liver transplantation. *Kidney Int Suppl* 1999;72:S71-74

35   Richardson D. Dialysis in non-renal organ (liver) transplantation. *Nephron* 2001;88:296-306

36   Morales JM. Management and prevention of acute renal failure in solid organ transplantation. *Ren Fail* 1996; 18:481-488

37   Manasia AR, Leibowitz AB, Miller CM, Silverstein JH, Schwartz M, Delgiudice R, Vallabhajosula S, Oropello JM, Benjamin E. Postoperative intravenous infusion of alprostadil (PGE1) does not improve renal function in hepatic transplant recipients. *J Am Coll Surg* 1996; 182:347-352

38   Nasraway SA, Klein RD, Spanier TB, Rohrer RJ, Freeman RB, Rand WM, Benotti PN. Hemodynamic correlates of outcome in patients undergoing orthotopic liver transplantation. Evidence for early postoperative myocardial depression. *Chest* 1995;107:218-224

39   Bilbao I, Charco R, Balsells J, Lazaro JL, Hidalgo E, Llopart L, Murio E, Margarit C. Risk factors for acute renal failure requiring dialysis after liver transplantation. *Clin Transplant* 1998; 12:123-129

40   Bartosh SM, Alonso EM, Whitington PF. Renal outcomes in pediatric liver transplantation. *Clin Transplant* 1997; 11:354-360

41   Cacciarelli TV, Esquivel CO, Moore DH, Cox KL, Berquist WE, Concepcion W, Hammer GB, So SKS.Factors affecting survival after liver transplantation in Infants. *Transplatation* 1997;64:242-248

42   Neuberger J, Gunson B, Komolmit P, Davies MH, Christensen E. Pretransplant prediction of prognois after liver Transplantation in primary sclerosing cholangitis using a Cox regression model. *Hepatology* 1999;29:1375-1379

43   Gonzalez FX, Rimola A, Grande L, Antolin M, Garcia-Valdecasas JC, Fuster J, Lacy AM,Cugat E, Visa J, Rodes J. Predictiver factors of early postoperative graft function in human liver transplantation. *Hepatology* 1994;20:565-573

44   Wong T, Devlin J, Roland N, Heaton N, Williiams R. Clinical characteristics affecting the outcome of liver transplantation. *Transplantation* 1997;64878-64888

45   Lo CM, Shaked A, Busuttil RW. Risk factors liver transplantation across the ABO barrier. *Transplantation* 1994; 58: 543-548

46   Figuras J, Busquets J, Grande L, Jaurrieia E, Perez-Ferreiroa J, Mir J, Margarit G, Loper P, Vazquez J, Casanova D, Bernardos A, De-Vicente E, Parrilla P, Ramon JM, Bou R. The deleterious effect of donor hight plasma sodium and extended preservation in liver transplantation. A multivariate analysis. *Transplantation* 1996;61:410-413

47   Chavez-Cartaya R, Rasmussa A, Tokat Y, Jamieson NV. Effect of preservation time on early graft function And outcome of orthotopic liver transplants. *Transplant Proc* 1995;27:724

48   Strasberg SM, Howard TK, Molmenti EP, Hretl M. Selecting the door live, risk factors for poor function after orthotopic liver transplantation. *Hepatology* 1994;20:829-838

49   Garcia S, Roque J, Ruza F, Gonzalez M, Madero R, Alvarado F, Herruzo R. Infection and associated risk factors in the immediate postoperative period of pediatric liver transplantation: a study of 176 transplants. *Clin Transplant* 1998; 12:190-197

50   Doyle HR, Morelli F, Mc Michael J,. Hepatic retransplantation: an analysis of risk factor associated with outcome. *Transplantation* 1996; 61: 1499-1505

51   Goss JA, Shackleton CR, McDiarmid SV. Long-term results of pediatric liver transplantation. An analysis of 569 transplants. *Ann Surg* 1998; 228:411-420

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