Conclusions PBC patients are at high risk of waiting list mortality in the current allocation system. MELD-based allocation could reduce this risk.

Keywords: Child–Turcotte–Pugh · Liver transplantation · Model for End-Stage Liver Disease

Introduction

Liver transplantation is the only curative treatment option with excellent long-term results in patients with end-stage liver diseases. At present, the number of patients waiting to undergo liver transplantation is increasing in Japan, as well as in both Europe and the United States. However, many patients are dying on the waiting list because of the donor organ shortage. For example, recent waiting list mortality was reported as being 22.8 % in the United States [1]. Management of liver transplant waiting lists is aimed at minimizing waiting list deaths by prioritization of those with a higher mortality risk, and by ensuring allocation of available organs to these patients. Therefore, prioritization and allocation decisions require the accurate prediction of the survival probability of patients.

The indications for liver transplantation include a wide variety of liver diseases, including viral hepatitis, autoimmune hepatitis, cholestatic disease, metabolic disorders, and hepatic neoplasms. Because each type of liver disease has disease-specific therapeutic options and associated risk of complications, liver disease etiology can influence the patient's natural disease course and risk of death. Moreover, disease-specific clinical tools are widely used to determine prognosis in patients with primary biliary cirrhosis (PBC) [2, 3] and primary sclerosing cholangitis [4]. However, it is uncertain whether patients waiting for liver transplantation have a disease-specific risk for waiting list mortality, and whether the ability of the currently used allocation system to assess the urgency of transplantation could be generalized to every patient with heterogeneous etiology.

By consensus, a disease severity index used to allocate liver donor organs should be able to predict the probability of death in patients with end-stage liver diseases of heterogeneous etiology. In the United States, where a large number of patients are registered for liver transplantation, the Child–Turcotte–Pugh (CTP) score [5] was initially applied to assess the severity of liver disease in the United Network for Organ Sharing (UNOS) allocation algorithms, because of its simplicity and recognized ability to assess prognosis in patients with heterogeneous chronic liver disease. Subsequently, a number of studies have demonstrated the accuracy of the Model of End-Stage Liver Disease (MELD) score [6] in predicting short-term mortality risk in patients with end-stage liver disease [7–9]. Since February 2002, the MELD score has therefore been used as a UNOS criterion for allocating organs to patients waiting for liver transplantation [10].

On the other hand, in the countries with a small number of registrations for liver transplantation, a system of prioritization based on a detailed clinical review, which includes CTP score, MELD score, and other disease-specific prognostic scores, as well as patients' demographics, laboratory data, and disease histories, by a small number of expert clinicians is likely to be used to judge disease severity and potential mortality accurately. This clinical judgment-based prioritization of patients awaiting liver transplantation was initiated in October 1997 in Japan and, at present, little information is available concerning the prognostic ability of this allocation system.

The aims of the present retrospective study were: (1) to clarify the disease-specific risk for waiting list mortality in patients waiting for liver transplantation; and (2) to compare the current system of waiting list prioritization and organ allocation in Japan with the MELD and CTP scoring systems with regard to the risk in PBC patients, who have the highest risk of waiting list mortality.

Patients and methods

Patients and liver allocation policy in Japan

This was a nationwide retrospective cohort study. We used the Japan Organ Transplant Network (JOT)/the Assessment Committee of Indication for Transplantation database to identify all patients listed for deceased donor liver transplantation in Japan between October 15, 1997 and August 31, 2011. We excluded patients who were less than 18 years of age because they had a spectrum of primary diagnoses substantially different from those of patients older than 18 years. We also excluded patients listed for retransplantation to ensure that all observations represented unique individuals. Finally, we excluded patients who were diagnosed with acute liver failure because these patients rarely have chronic liver disease and are assigned the highest priority.

For JOT registration, the demographic, clinical, and laboratory data including CTP score, MELD score, or disease-specific prognostic score of all candidates are reviewed, and each candidate is assigned a clinical priority by the Assessment Committee of Indication for Transplantation (four physicians, five surgeons, and one pediatrician). The priority of candidates is represented by a medical point system, in which points are awarded according to estimated survival: 9 points for estimated survival <30 days, 6 points for <180 days, 3 points for

<360 days, and 1 point for ≥360 days. In patients with hepatocellular carcinoma, the points were determined only by the degree of hepatic decompensation. Additional points are awarded according to ABO blood group compatibility: 1.5 points for an identical blood group and 1 point for a compatible blood group. Patients with higher total points have a higher priority for donor liver allocation. For patients with identical points, waiting time is a liver allocation measure.

Age of the patient, blood type, etiology of liver disease, and medical point at listing were available for all the patients. Detailed demographic, clinical, laboratory data, including CTP score and MELD score at the time of listing, were available only in patients registered since June 22, 2006. The CTP score uses two clinical variables (ascites and encephalopathy), and three laboratory parameters (serum bilirubin and albumin levels and prothrombin time). Each variable is assigned a score from 1 to 3, with the aggregate score representing the CTP score [5]. Although the original CTP score used different criteria for total bilirubin level between patients with cholestatic disease and those with other etiologies, the criteria for the CTP score in the current Japanese allocation system did not change according to the etiology of liver disease. The MELD score was calculated using the most recent version of the formula documented on the UNOS website [11]: $9.57 \times \log_e$(creatinine mg/dL) $+ 3.78 \times \log_e$(bilirubin mg/dL) $+ 11.2 \times \log_e$(international normalized ratio [INR]) $+ 6.43$, rounded to the nearest integer. Liver disease etiology was not incorporated in this version of the formula. Laboratory values less than 1.0 were set to 1.0 and the maximum serum creatinine was set to 4.0 mg/dL. The serum creatinine was set to 4.0 mg/dL if the patients had received dialysis at least twice within the week prior to the serum creatinine test. The MELD score was not capped at a score of 40. In PBC patients, the spontaneous survival predicted by the updated Mayo model was calculated as described previously [3].

Outcome

The patients' follow-up ended on 30 September 2011. The primary endpoint "waiting list mortality" or "waiting list death" was a combination of death and removal from the waiting list because the patient became too sick for transplantation or was otherwise medically unsuitable. We considered patients who were removed from the transplant list on account of clinical deterioration to be equivalent to patients who died, because these chronic liver diseases are almost uniformly fatal in the short term without transplantation. All other outcomes were censored, with the most common censoring events being transplantation or list removal due to an improvement in the patient's condition resulting in the patient no longer requiring transplantation.

Statistical analysis

Cox proportional hazards ratios (HRs) with 95 % confidence intervals (CI) for waiting list mortality were estimated with univariate models using age, gender, blood type, etiology of liver disease, as well as multivariate models using age and etiology of liver disease. To compare patients' characteristics between chronic hepatitis C virus (HCV) infection and PBC, we used the Mann–Whitney *U* test for numerical variables or the chi-square test for categorical variables. The HRs with 95 % CI for waiting list mortality of PBC patients were adjusted for each disease severity index, such as medical point, CTP score, and MELD score by bivariate Cox proportional hazards models. The rates of survival were estimated by the Kaplan–Meier method, and compared by log-rank test. All analyses were conducted using IBM SPSS version 19 (IBM SPSS, Chicago, IL, USA). A P value below 0.05 was considered to be statistically significant.

Results

Patient characteristics and outcome

A total of 1,407 patients were listed for deceased donor liver transplantation through the JOT registry during the study period. Of these patients, 1,295 (92.0 %) were aged ≥18 years. The etiology of liver disease in these subjects is shown in Table 1. The most prevalent diagnoses in patients ≥18 years were HCV infection (254 of 1,295, 19.6 %), hepatitis B virus infection (157 of 1,295, 12.1 %), and PBC (156 of 1,295, 12.0 %), and these accounted for 43.7 % of all patients ≥18 years. Of 1,295 patients, 239 were excluded from the study: 142 for acute liver failure and 97 for repeat liver transplant. Thus, a total of 1,056 patients formed the study cohort. In the study cohort, 64 % of patients were men and the median age of all patients was 51 years (range, 18–69 years). At listing, 78 patients were registered at medical point 1, 297 at point 3, 682 at point 6, and 29 at point 9. A flow diagram of the patient outcomes is shown in Fig. 1. At the end of study period, 313 patients were still listed and 743 had been removed from the list, with 267 removed for liver transplantation, 378 for death, and 98 for other reasons, including 54 who were too sick, 11 for improvement in their condition, and 33 for an unknown reason. Of the 267 patients who received liver transplantation, only 81 cases were able to receive deceased donation in Japan, and this accounted for 10.9 % of all patients removed from the list. Waiting list mortality, a combination of death and becoming too sick for transplantation, accounted for 58.1 % of all the patients removed from the list.

Factors associated with waiting list mortality

In univariate analysis, age, biliary atresia, PBC, hepatocellular carcinoma, metabolic diseases, polycystic diseases, and vascular diseases showed statistically significant association with waiting-list mortality. In multivariate analysis, age (HR 1.04; 95 % CI 1.03–1.05, $P < 0.001$), PBC (HR 1.79; 95 % CI 1.34–2.39, $P < 0.001$), and polycystic diseases (HR 0.27; 95 % CI 0.10–0.73, $P = 0.01$) were independently associated with waiting list mortality (Table 2). Hence, PBC patients had a 79 % higher risk of waiting list mortality compared with HCV patients with adjustment for age.

Table 1 Etiology of liver disease

	Total (n = 1,407)	≥18 years (n = 1,295)	<18 years (n = 112)
Cholestatic diseases	381	325	56
BA	93	48	46
PBC	156	156	0
PSC	105	99	6
Caroli disease	8	7	1
Others	18	15	3
Hepatocellular diseases	567	565	2
HCV	254	254	0
HBV	157	157	0
HCV and HBV	8	8	0
Alcoholic	48	48	0
AIH	22	22	0
NASH	25	25	0
Cryptogenic cirrhosis	53	51	2
HCC	76	76	0
Acute liver failure	163	142	21
Graft failure	121	97	24
Vascular disease	12	12	0
Metabolic disease	62	53	9
Polycystic disease	24	24	0
Others	1	1	0

AIH autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

Waiting list mortality of PBC patients

The Kaplan–Meier waiting list survival curves for all PBC and HCV patients are shown in Fig. 2. The 1- and 2-year survival probabilities in HCV patients were 63 and 49 %, respectively (median 631 days, 95 % CI 355–907 days), whereas those in PBC patients were 51 and 33 %, respectively (median 392 days, 95 % CI 283–500 days); the differences between them represented a statistically significant difference (log-rank test, $P < 0.001$). Detailed demographic and clinical characteristics were available in 189 of 254 HCV patients and 81 of 156 PBC patients who were registered after June 2006. A comparison of the characteristics of patients with PBC and HCV is shown in Table 3. In comparison with HCV patients, PBC patients were younger and predominantly female. Patients with PBC had significantly higher platelet counts and serum bilirubin values, and lower INR and serum creatinine values. Neither the CTP score nor the medical point at listing was different between the groups. Conversely, the MELD score at listing was significantly higher in patients with PBC than in those with HCV. In addition, the median of the updated Mayo risk score was 9.4 in the PBC patients, and this predicted 1- and 2-year spontaneous survival rates of 74 and 54 %, respectively.

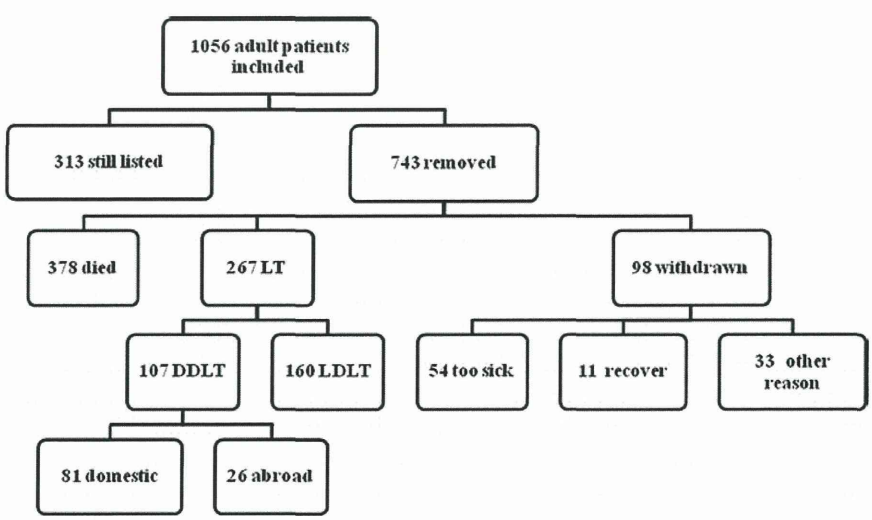

Fig. 1 Flow diagram of patient outcomes. *DDLT* deceased donor liver transplantation, *LDLT* living donor liver transplantation, *LT* liver transplantation

Table 2 Univariate and multivariate analysis of variables associated with waiting list mortality

Variables	Univariate			Multivariate		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age (per year of age)	1.04	1.03–1.05	<0.001	1.04	1.03–1.05	<0.001
Male gender	0.93	0.77–1.13	0.48			
Blood type						
A	1.00	Reference				
B	1.07	0.83–1.43	0.61			
O	1.13	0.90–1.43	0.29			
AB	1.26	0.90–1.77	0.17			
Etiology						
HCV	1.00	Reference				
BA	0.40	0.22–0.72	0.002			
PBC	1.62	1.21–2.16	0.001	1.79	1.34–2.39	<0.001
PSC	0.79	0.54–1.17	0.24			
HBV	0.77	0.56–1.05	0.10			
Alcohol	0.95	0.59–1.53	0.83			
AIH	0.77	0.34–1.74	0.52			
NASH	1.11	0.76–1.63	0.59			
HCC	1.46	1.05–2.05	0.003			
Metabolic disease	0.40	0.22–0.75	0.004			
Polycystic disease	0.26	0.10–0.70	0.008	0.27	0.10–0.73	0.01
Vascular disease	0.009	0.01–0.67	0.002			
Others	0.70	0.34–1.43	0.33			

AIH autoimmune hepatitis, *BA* biliary atresia, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HR* hazard ratio, *NASH* non-alcoholic steatohepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis

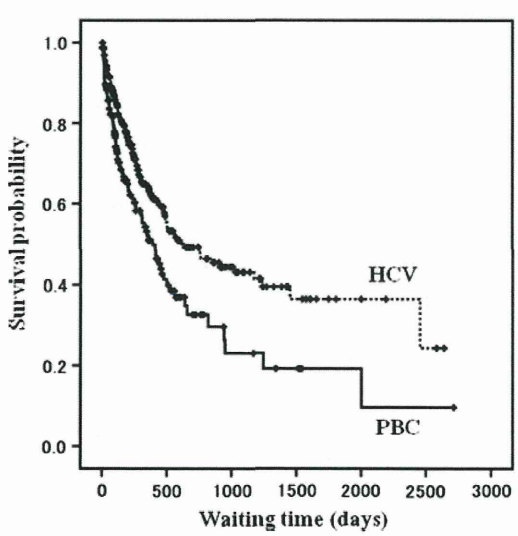

Fig. 2 Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV, $n = 254$) and primary biliary cirrhosis (PBC, $n = 156$)

Table 3 Comparison of patient characteristics between HCV and PBC

Variable	HCV ($n = 189$)	PBC ($n = 81$)	*P* value
Age (years)	55 (29–69)	52 (27–69)	0.02[a]
Gender (male/female)	143/46	15/66	<0.001[b]
Platelet count ($\times 10^4/\mu L$)	6.0 (1.7–49.0)	10.2 (2.2–42.3)	<0.001[a]
Albumin (g/dL)	2.8 (1.8–4.4)	2.8 (1.4–4.2)	0.96[a]
Total bilirubin (mg/dL)	2.7 (0.4–39.8)	7.2 (0.7–41.2)	<0.001[a]
Creatinine (mg/dL)	0.78 (0.4–7.4)	0.67 (0.37–2.83)	<0.001[a]
Prothrombin time (%)	54.7 (11.0–103.0)	62.2 (16.0–120.0)	0.001[a]
INR	1.51 (0.98–6.24)	1.32 (0.91–4.31)	0.001[a]
MELD score	15 (7–52)	17.5 (8–39)	0.002[a]
CTP score	10 (6–15)	10 (5–15)	0.27[a]
Medical point (1, 3/6, 9)	54/135	22/59	0.81[b]

Data are shown as median (range). Data were available for patients who were listed after June 22, 2006

CTP Child–Turcotte–Pugh, *HCV* hepatitis C virus, *INR* international normalized ratio, *MELD* model of end-stage liver disease, *PBC* primary biliary cirrhosis

[a] Mann–Whitney *U* test

[b] Chi-square test

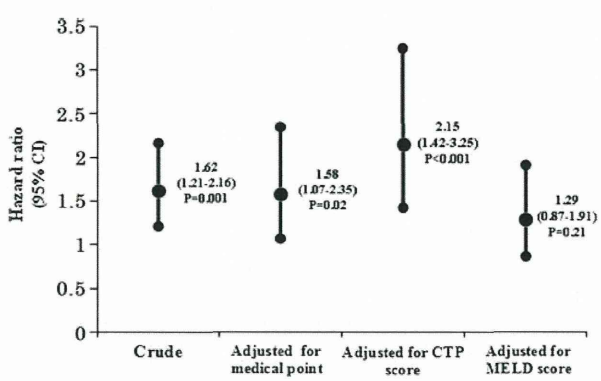

Fig. 3 Adjusted risk of waiting list mortality for patients with primary biliary cirrhosis compared with patients with chronic hepatitis C

To examine which disease severity index was able to assess the risk of PBC patients accurately, we estimated their relative hazards with adjustment for each index. We did not estimate age-adjusted relative hazard because age was not included in the allocation measures. Figure 3 indicates the crude and disease severity index-adjusted HR for waiting list mortality of PBC patients with reference to HCV patients. In univariate analysis, PBC patients were at 62 % (HR 1.62; 95 % CI 1.21–2.16, $P = 0.001$) increased risk of waiting list mortality

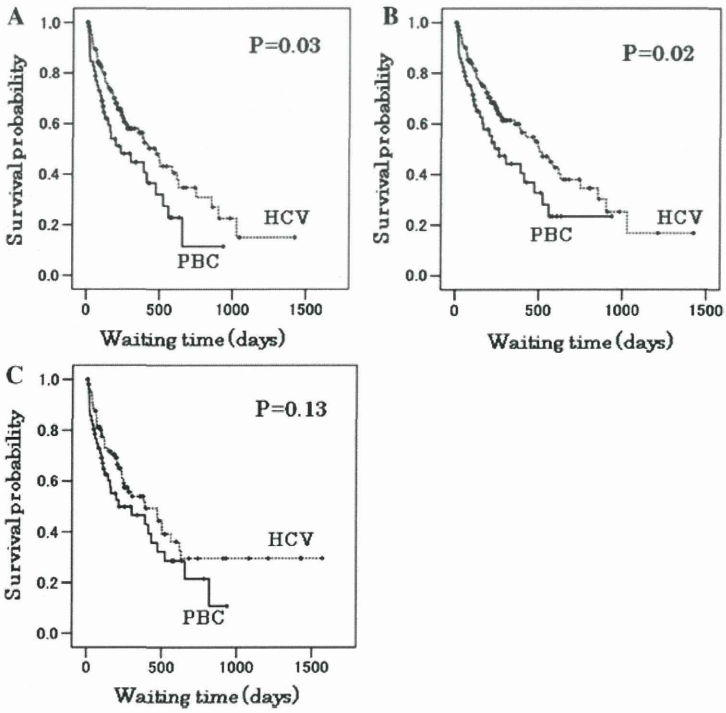

Fig. 4 Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV) and primary biliary cirrhosis (PBC). Patients stratified medical point = 6 (**a**), and Child–Turcotte–Pugh score ≥10 (**b**), and Model of End-Stage Liver Disease (MELD) score ≥15 (**c**)

compared with HCV patients. In bivariate analysis, the medical point-adjusted HR of waiting list mortality of PBC patients was significantly higher than that of HCV patients (HR 1.58; 95 % CI 1.07–2.35, $P = 0.02$). The CTP score-adjusted HR also showed a significantly increased risk of waiting -list mortality in PBC patients (HR 2.15; 95 % CI 1.42–3.25, $P < 0.001$). However, the MELD score-adjusted HR did not show a statistically significant risk of waiting list mortality in PBC patients (HR 1.29; 95 % CI 0.87–1.91, $P = 0.21$).

Waiting list survival of patients with HCV and PBC was compared with stratification by each of the disease severity indices (Fig. 4). Patients with medical point 6, for which most PBC and HCV patients were registered, showed a significantly shorter waiting list survival for PBC patients than of HCV patients (median 261 vs. 503 days, $P = 0.02$). In patients with CTP score ≥10, the score classified as C, the shorter waiting list survival of PBC patients was also significant (median 235 vs. 475 days, $P = 0.03$). On the other hand, when they were selected by MELD ≥15, the score indicating patients who can be expected to achieve improved survival with liver transplantation [12], there was no significant difference in the waiting list survival rate between them ($P = 0.13$).

Discussion

The result of this study clearly indicated that the most common reason for removal from the waiting list in Japan was "waiting list death", which was a combination of death and becoming too sick for transplantation. The waiting list death included 58.1 % of all the patients removed from the list. In the United States, a recent report indicated that waiting list death was the reason for removal from the list in 25.9 % of adult patients [1]. Although this report included patients with acute liver failure and re-transplantation, high waiting list mortality in Japan was evident. Thus, the high mortality rate on the liver transplant waiting list is a major challenge in Japan. Moreover, severe donor organ shortage in Japan should contribute to the high waiting list mortality [13]; an improved organ allocation policy will be necessary to cause a decrease in waiting list death.

In this study, we found that PBC patients had a significantly higher risk of waiting list mortality compared with patients with other etiologies in the JOT registry. Since PBC is currently the third most common diagnosis in the JOT registry for liver transplantation, poor waiting list survival of PBC patients would contribute to the high waiting list mortality in Japan. PBC is a cholestatic liver disease that causes bile duct deterioration and progresses slowly to a terminal phase characterized by hyperbilirubinemia, signs of decompensated cirrhosis, ascites, and variceal bleeding. Only one type of medical therapy, involving the use of ursodeoxycholic acid (UDCA), is now widely recognized to improve the prognosis of PBC patients. Many studies have shown that UDCA therapy not only improves biochemical indices, but also delays histologic progression and improves survival without transplantation [14–16]. However, evidence has also accumulated that the

favorable effect of UDCA therapy is limited to patients with early-stage disease. In histologically advanced patients or biochemical non-responders, the transplant-free survival rate of UDCA-treated patients was not different from spontaneous survival [16, 17]. This means that PBC patients have no effective medical therapeutic option to prolong their survival when they have progressed to end-stage liver disease, and liver transplantation remains the only hope of a cure [18, 19]. PBC patients in our cohort also showed a consistently poor survival of a median period of 392 days.

The reason why PBC patients have a higher risk for waiting list mortality compared with patients with other etiologies of chronic liver disease is not clearly understood. Interestingly, PBC patients were younger, and their INR and serum creatinine levels were lower than for HCV patients at registration. This indicated that neither age nor liver and renal function at registration alone caused poor waiting list survival of PBC patients; the registration of PBC patients was not later than that for HCV patients. The rate of disease progression and lethal complications might be involved in their short waiting list survival rate. Moreover, the actual waiting list survival rate in PBC patients was not greater than the updated Mayo score-predicted spontaneous survival rate. This observation indicated that the PBC patients on the waiting list were refractory to the medical therapy and their waiting list survival suddenly deteriorated. Further analyses, particularly on the cause of death, are required to clarify the pathophysiology of PBC patients who have progressed to end-stage liver disease.

In general, deceased donor livers are allocated for transplantation on the basis of "sickest first", i.e., those who are more likely to die without a liver transplantation are assigned the highest priority. Therefore, the disease severity index used in the liver allocation system should consider the urgency of PBC patients for liver transplantation. However, our results have clarified the inability of the currently used Japanese allocation system to identify the risk of PBC patients. The medical point-adjusted HR of PBC patients revealed that they were at 58 % increased risk of waiting list mortality compared with HCV patients. In addition, the CTP score-adjusted HR showed that PBC patients were at 115 % increased risk for waiting list mortality. Thus, it is not only the current allocation system but also the CTP score-based allocation that cannot capture the risk for waiting list mortality in PBC patients. On the other hand, we found that the MELD score-adjusted HR of PBC patients lost statistical significance, and stratification by MELD score revealed comparable survival curves between patients with PBC and HCV. These results indicated that PBC patients had a similar risk of waiting list mortality compared with patients with other etiologies when they were stratified by MELD score. At the time of registration, the patients with HCV and PBC had different characteristics; however, only the MELD score accurately evaluated their disease severity, and therefore, MELD-based allocation would adequately assign priority to the patients according to their risk of waiting list mortality. Thus, our results demonstrated that the MELD score was superior to both the current Japanese allocation and CTP score-based allocation for ranking patients in the JOT registry by their risk of waiting list mortality.

In addition, patients should be re-evaluated according to their chronological change of hepatic failure to improve allocation. However, most patients with chronic liver disease were waiting at medical point 6 as an upper limit, because the highest priority at medical point 9 was generally awarded to the patients with acute liver failure or early graft failure in the current Japanese allocation system. Therefore, the current allocation system did not completely reflect the chronological change in the degree of liver failure. Thus, the MELD score, which was expressed numerically as a continuous variable with a wide dynamic range in the evaluation of hepatic decompensation, would have an advantage over the medical point system for assessing the chronological change in patients' risk of death.

In conclusion, this study demonstrated that patients with PBC, the third most common indication for liver transplantation in Japan, have a high risk for waiting list mortality in the current Japanese allocation system. The allocation system should be changed to accurately prioritize the patients with a higher mortality risk; MELD-based allocation would be suitable for this purpose and could reduce the waiting list mortality of PBC patients.

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Conflict of interest The authors declare that they have no conflict of interest.

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今月のテーマ　PBC診療の最前線

原発性胆汁性肝硬変に対する肝移植

玄田拓哉　市田隆文[1)]

要旨：原発性胆汁性肝硬変（primary biliary cirrhosis；PBC）は肝移植の主要な適応疾患のひとつである．近年は，内科的治療の進歩のためか，欧米でのPBC移植数は減少傾向にある．しかし，末期肝硬変に至ったPBCでは，現在でも肝移植は唯一の救命法であり，適切な移植時期は予後予測モデルなどから計られる．移植成績は他の疾患と比較して良好で，5年生存率はいずれの報告でも70%を越える．また，その成績に生体ドナーと脳死ドナーの差は認められない．PBCは移植後グラフト肝に再発するが，頻度，危険因子，長期予後など不明な部分もいまだに多い．

索引用語：原発性胆汁性肝硬変，肝移植，予後予測，成績，再発

はじめに

原発性胆汁性肝硬変（primary biliary cirrhosis；PBC）は，小葉間胆管障害による進行性の肝内胆汁うっ滞による肝障害をきたし，緩除に進行して高度の黄疸，腹水，静脈瘤出血を呈する非代償性肝硬変に至る原因不明の疾患である．臨床症状を認めない無症候性PBCの場合，10年生存率は50%から70%と高いが，臨床症状を有する症候性PBCの場合，生存期間の中央値は5年から8年と報告されている[1)2)]．主な死因は，肝不全か門脈圧亢進症による食道静脈瘤破裂とされ[3)]，組織学的に進行した例では肝細胞癌の合併もあり得る[4)]．いまだに根治的治療は確立されていないが，ウルソデオキシコール酸（ursodeoxycholic acid；UDCA）はPBCの進行抑制効果が複数のランダム化比較試験で確認されており，臨床現場では第一選択薬として用いられている．UDCAの継続的な内服はPBC患者の生化学検査値を改善させるばかりでなく，組織学的な進行を遅らせ生存率の改善をもたらすことが明らかになっているが[5)〜7)]，その予後改善効果はすべてのPBC患者にもたらされるわけではない．組織学的に進行してから投与を開始した例や，UDCA投与によっても生化学検査結果の改善効果が乏しい例の生存率は，無治療例の生存率と差がないことが判明している[7)8)]．すなわち，PBC患者が末期肝硬変まで進行した段階では予後を改善する有効な内科的治療法はなく，肝移植のみが唯一の救命法となる．本稿ではPBCに対する肝移植の現況を概説した．

I　PBCに対する肝移植の動向

PBCによる末期肝硬変は，肝移植が臨床応用された初期から主要な適応疾患のひとつであった．1980年代に報告されたIwatsukiら[9)]の1000例の肝移植の中でPBCは適応疾患の16.5%を占め，二番目に頻度の高い適応疾患であった．ELTR（European Liver Transplant Registry）による1988年から2001年までの欧州全体の統計では，

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Liver transplantation for primary biliary cirrhosis

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PBCは全移植症例39196例中2969例（8%）を占め，アルコール性肝硬変，C型肝硬変，急性肝不全に次ぐ頻度となっている[10]．米国のOPTN（Organ Procurement and Transplant Network）の最も新しい統計報告によると，2009年12月末時点でPBCを含む胆汁うっ滞性疾患は，脳死肝移植待機している成人患者の7.9%を占めている[11]．これらの報告からわかるように，初期の頃と比較して最近では移植適応疾患に占めるPBCの割合は減少傾向にある．移植適応疾患が変化したことも一因かもしれないが，欧州においても米国においても肝移植数全体は増加傾向にあるにもかかわらず，PBCの肝移植自体は，全体に対する割合のみならず絶対数も減少傾向にある[12][13]．興味深いことに，同じ肝内胆汁うっ滞性疾患である原発性硬化性胆管炎（primary sclerosing cholangitis；PSC）の割合はほぼ不変であり，このようなPBCに対する肝移植数の減少傾向はUDCAの治療効果によりもたらされたものではないかと考えられている．

わが国において行われた世界初の成人生体肝移植は，PBC患者に対して行われた[14]．このことからもわかるように，PBCは日本においても肝移植が臨床現場に広まるきっかけとなった，重要な適応疾患である．わが国では脳死肝移植普及の遅れから，この成功を契機にして生体肝移植が爆発的に広まった．2010年末までの累計移植数では脳死肝移植95例に対し生体肝移植は6097例であり，わが国の肝移植は98.5%が生体ドナーからの提供で行われた計算になる．このうち2010年末までに初回成人生体肝移植は3796例に行われたが，その中でPBC症例は535例14%を占めており，PBCが本邦でも肝移植の主要な対象疾患であることがわかる[15]．PBCの移植全体に対する頻度は欧米と比較してやや高い印象であるが，各統計の詳細を比較すると欧米において頻度の高いアルコール性肝硬変がわが国ではほとんどなく，このためにPBCの相対的な割合が日本で高くなっているのではないかと考えられる．

II PBCの移植適応と移植時期

PBCによる肝硬変の移植適応は難治性腹水，繰り返す静脈瘤からの出血や肝性脳症，（ミラノ基準内の）肝細胞癌の合併など，その他の疾患による肝硬変と変わるところはない．それ以外に，胆汁うっ滞性肝障害に比較的特徴的な皮膚掻痒感や慢性的な倦怠感も，はなはだしい場合はPBC患者の生活の質（quality of life；QOL）を著しく障害するため，移植適応となる場合がある[16][17]．

Table 1. Child-Turcotte-Pugh（CTP）スコア

points	1	2	3
Encephalopathy	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin（mg/dL）	1～2	2～3	>3
Albumin（g/dL）	>3.5	2.8～3.5	<2.8
INR	<1.7	1.7～2.3	>2.3
For PBC：bilirubin	1～4	4～10	>10

一般に肝移植は，移植を受けない場合に予想される生存率を移植後に期待し得る生存率が上回るタイミングで行われる．食道静脈瘤に対する食道離断術のリスク評価のために作成されたChild-Turcotte-Pugh（CTP）スコア（Table 1）[18][19]や，経静脈的肝内門脈大循環短絡術後の予後予測のために作成されたmodel for end-stage liver disease（MELD）スコアは（Table 2）[20]，慢性肝疾患の一般的予後予測スコアとして有用性と汎用性が認められている．これらのスコアを用いると，CTPスコアが7もしくはMELDスコアが15を越えた場合に，移植を受けた場合の生存率が移植を受けない場合の生存率を上回ると判断され，肝移植の施行が推奨される[21]．

PBCは症例間で自然経過の差が少ないため，さまざまな予後予測モデルの作成が試みられてきた．Mayo Clinicにおいて中央値5.5年の経過観察を受けた無治療PBC 312例のデータを用いて同定された因子から作成された予後予測式がMayo natural history modelで，年齢，血清ビリルビン値，アルブミン値，プロトロンビン時間，浮腫の有無，利尿薬の有無から計算される（Table 2）[22]．Mayo modelから得られたリスクスコア（R）で7年後までの予測生存率が計算可能であり，このモデルの有用性は，Mayo Clinicにおける別の

Table 2. PBCに用いられる予後予測式

1. Model for end-stage liver disease (MELD) score
   $9.57 \times \log_e$ (creatinine mg/dL) $+ 3.78 \times \log_e$ (bilirubin mg/dL) $+ 11.2 \times \log_e$ (international normalized ratio [INR]) $+ 6.43$.
   Laboratory values less than 1.0 were set to 1.0 and the maximum serum creatinine was set to 4.0 mg/dL.

2. The Mayo natural history model for PBC
   $R = 0.039$ (age) $+ 0.871 \log_e$ (bilirubin) $- 2.53 \log_e$ (albumin) $+ 2.38 \log_e$ (prothrombin time) $+$ 0.859 (edema*)
   *0 = no edema without diuretic therapy ; 0.5 = edema without diuretic therapy or edema resolved with diuretic therapy ; 1 = edema with diuretic therapy.
   (http://www.mayoclinic.org/gi-rst/mayomodel1.html)

3. The updated Mayo natural history model for PBC
   $R = 0.051$ (age) $+ 1.209 \log_e$ (bilirubin) $- 3.304 \log_e$ (albumin) $+ 2.754 \log_e$ (prothrombin time) $+$ 0.675 (edema*)
   (http://www.mayoclinic.org/gi-rst/mayomodel2.html)

4. 日本肝移植適応研究会の予後予測式
   $\lambda = -4.33 + 1.2739 \log_e$ (total bilirubin) $+ 4.4880 \log_e$ (AST/ALT)
   6カ月後の死亡確率 (%) $= 1/(1 + e^{-\lambda}) \times 100$

106例のPBC患者と，他の施設の176例で確認された[23]．それ以前に発表された予後予測式と異なり[21][25]，このMayo modelは変数に組織学的評価を含まないという臨床的に有利な点もあり，一般に広く用いられるようになった．また，自然経過による予後を予測するばかりでなく，移植前のリスクスコアが7.8を越えると移植後の死亡リスクが上昇し，集中治療室入室日数，在院日数，輸血量など医療資源の必要量も有意に増加することが示されており，このスコアを越える前の移植施行が適切とされている[26][27]．

Mayo modelにより得られるリスクスコアを時系列で観察すると，患者死亡の2年以上前は年率0.23の割合で増加するが，死亡の2年以内になるとその割合が年率1.4に急増することが判明した．この結果は，短期間で死亡するリスクの高い患者に対してはMayo modelが生存率を過大に評価している可能性を示している．そこでMurtaughらは患者の時系列での観察から得られたデータを用いてupdated Mayo modelを作成した(Table 2)[28]．このupdated modelは2年以内の生存予測に関しては元のmodelより優れていることが示されているため，短期的な予後予測にはupdated modelを用いることが勧められる．

一方，わが国では日本肝移植適応研究会において症候性PBC 141例を解析し，血清ビリルビン値とAST/ALTの2つを変数とする独自の予後予測式が作成されている (Table 2)[29]．現行のわが国の脳死肝移植レシピエント登録基準では，この日本肝移植適応研究会モデルでの死亡確率を用いて医学的緊急性に関する点数配分が行われる．

III PBCの移植成績

1980年代に，英国King's College病院のグループと米国Pittsburgh大学のグループが，予後予測モデルにより得られた予測生存と比較して実際の移植後生存が明らかに上回っていることを示し，末期肝硬変に至ったPBC患者に対する有効な治療としての肝移植が確立した[30][31]．1980年代前半のPBCに対する移植成績は1年生存率76%，2年生存率75%であったが，1990年代には周術期管理の進歩もあり，それぞれ93%，90%と更に改善している[26]．ELTRからの2001年までの統計では，欧州全体でPBCの生存率は移植後1年，5年，10年でそれぞれ83%，77%，69%