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Figure legends

Figure 1 Subjects in this study

Figure 2 Clinical course in recipients with acute rejection after delivery

MMF, mycophenolate mofetil. Acute rejection was diagnosed by second liver biopsy (rejection activity index, 4).

Figure 3 Receiver operating characteristic (ROC) curves in pregnant recipients

A, The age at pregnancy diagnosis and the pregnancy-induced hypertension; B, the interval from liver transplantation to pregnancy and fetal growth restriction; C, the interval and pregnancy-induced hypertension; D, the interval and extremely low birth weight

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Table 1. Indications for living donor liver transplantation

Diseases	No. of patients
Congenital biliary atresia	14
Acute hepatic failure	9
Primary sclerosing cholangitis	2
Autoimmune hepatitis	1
Hepatitis B virus	1
Budd-Chiari syndrome	1
Familial amyloid polyneuropathy	1
Hepatocellular carcinoma	1

Table 2. Interval from living donor liver transplantation to pregnancy and delivery outcomes (35 pregnancies in 27 recipients)*

Outcomes	Total	Interval <3 years	Interval ≥3 years	P
Age at pregnancy, median (range)	27 (22-41)	35 (24-41)	28 (22-40)	0.0014
Indications for liver transplantation				
Congenital biliary atresia	16	3	13	0.327
Acute hepatic failure	12	4	8	
Primary sclerosing cholangitits	1	1	0	
Others	6	2	4	
Complications during pregnancy	(n = 35)	(n = 10)	(n = 25)	
Spontaneous abortion	1 (2.9)	0	1 (4.0)	>0.999
Fetal death	3 (8.6)	2 (20.0)	1 (4.0)	0.190
Fetal growth restriction	7 (2.0)	5 (50.0)	2 (8.0)	0.0120
Liver dysfunction	4 (11.4)	2 (20.0)	2 (8.0)	0.561
Pregnancy-induced hypertension	6 (17.1)	5 (50.0)	1 (4.0)	0.0040
Delivery outcomes †	(n = 31)	(n = 8)	(n = 23)	
Preterm delivery	10 (28.6)	4 (50.0)	6 (26.1)	0.381
Cesarean delivery	12 (38.7)	4 (50.0)	8 (34.8)	0.676
Low birth weight (<2500g)	12 (38.7)	5 (6.3)	7 (30.4)	0.206
Extremely low birth weight (<1500g)	4 (12.9)	3 (3.8)	1 (4.3)	0.0432
Birth defects	2 (6.5)	1 (1.3)	1 (4.3)	0.456

*Three pregnancies (3 recipients) who underwent artificial abortion were excluded from analysis.
† Four pregnancies (4 recipients) with spontaneous abortion or fetal death were excluded from analysis. Numbers in parenthesis were percent.

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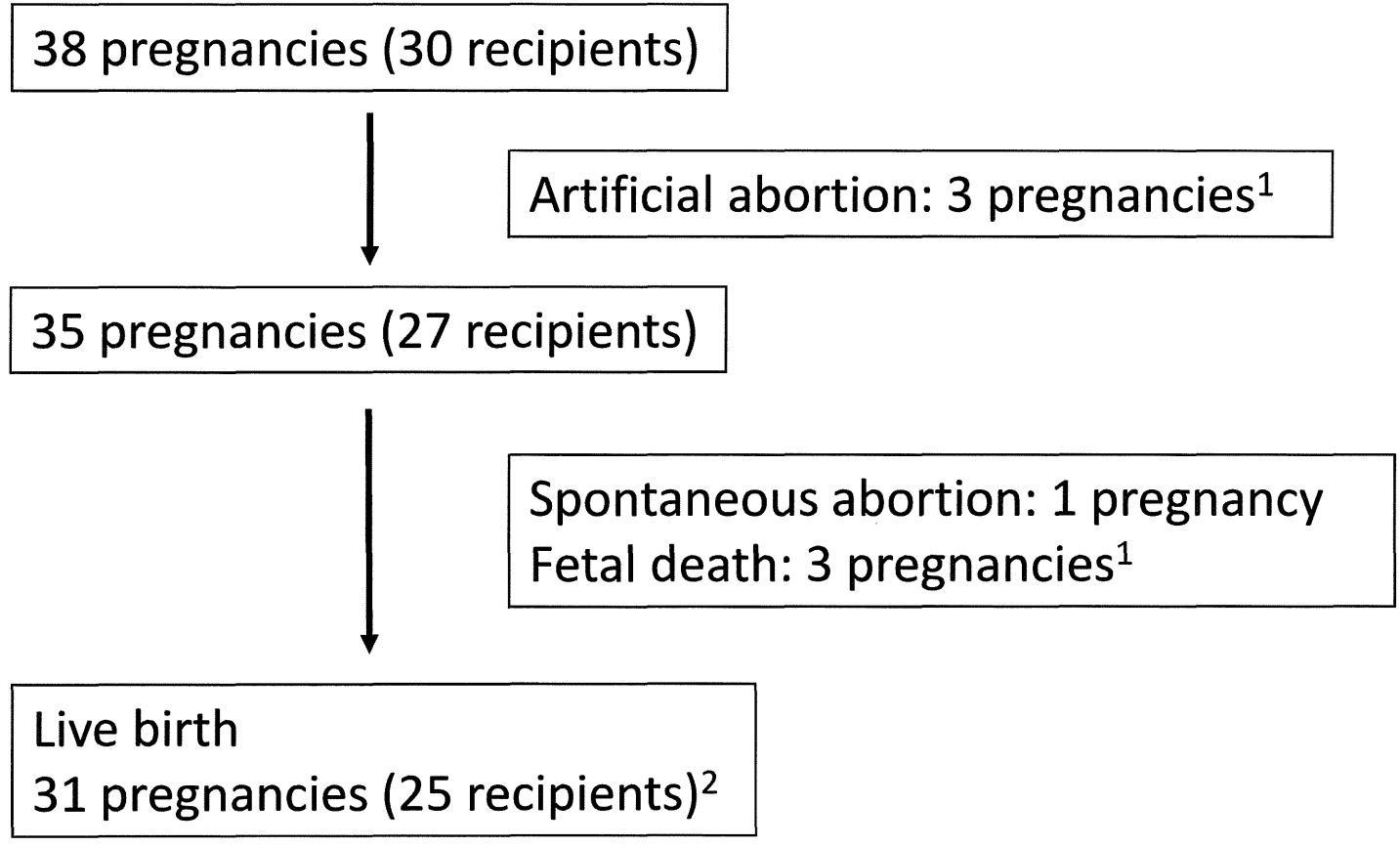
Fig. 1 Subjects in this study



[1]In one recipient, artificial abortion was performed at the first pregnancy and the second pregnancy was resulted in fetal death.
[2]Six recipients had live birth twice.

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Fig. 2

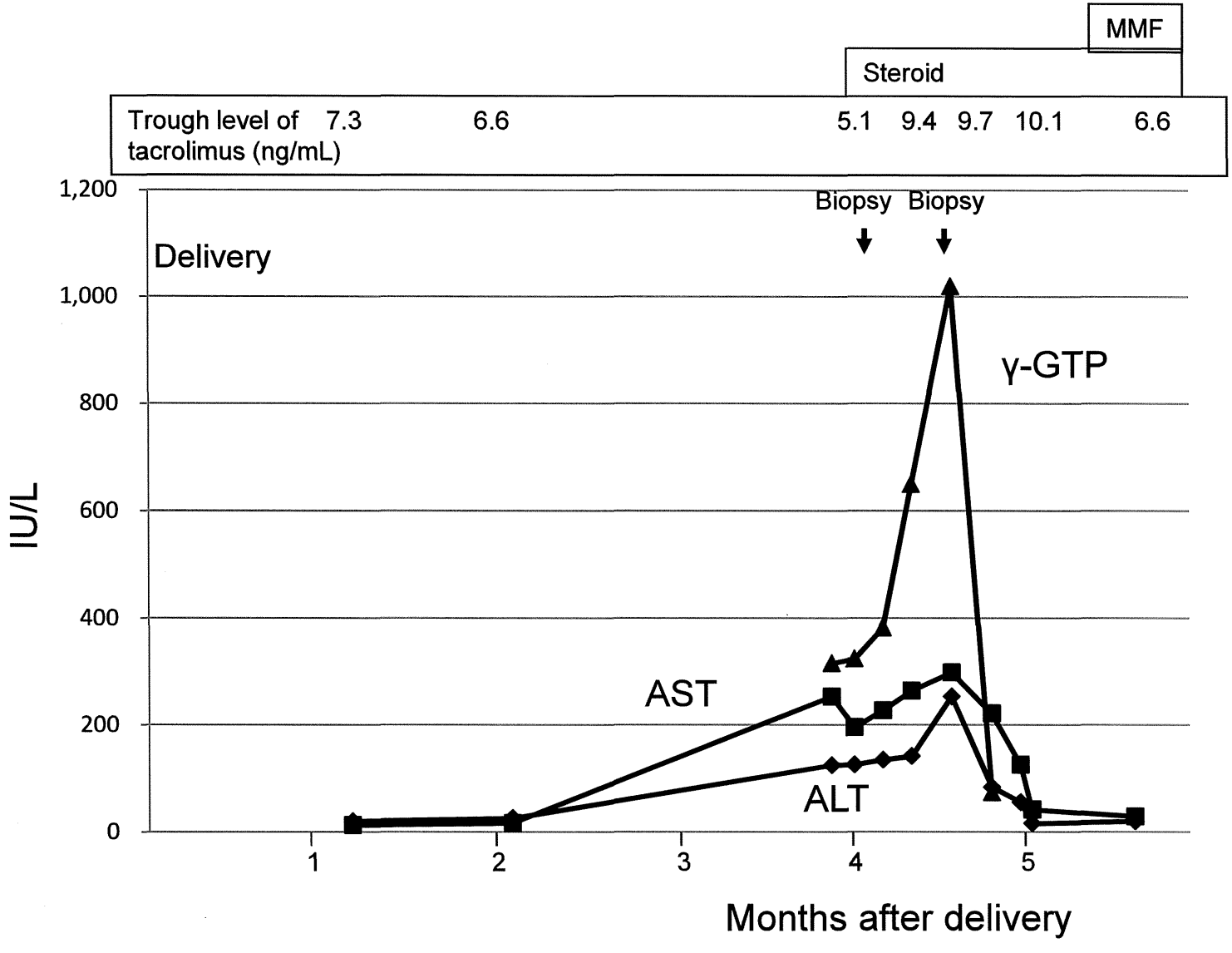
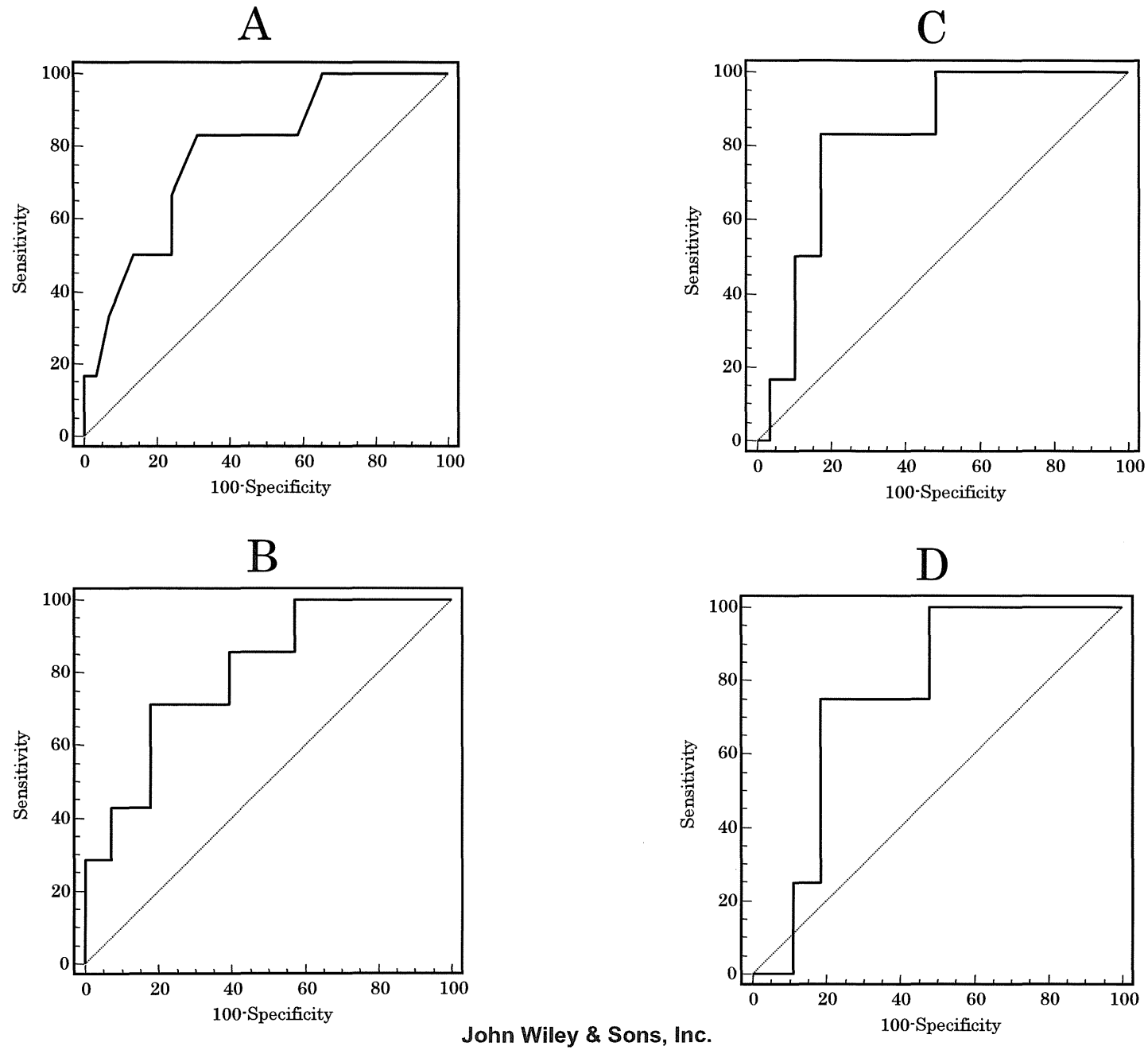

MMF
Steroid
Trough level of tacrolimus (ng/mL)
7.3
6.6
5.1
9.4
9.7
10.1
6.6
Biopsy
Biopsy
Delivery
γ-GTP
AST
ALT
IU/L
1,200
1,000
800
600
400
200
0
1
2
3
4
5
Months after delivery

Fig. 3



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The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Waiting list mortality of patients with primary biliary cirrhosis in the Japanese transplant allocation system

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Abstract

Background The present study aimed to evaluate etiology-based differences in the risk of waiting list mortality, and to compare the current Japanese transplant allocation system with the Child–Turcotte–Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scoring systems with regard to the risk of waiting list mortality in patients with primary biliary cirrhosis (PBC).

Methods Using data derived from all adult candidates for deceased donor liver transplantation in Japan from 1997 to 2011, we assessed factors associated with waiting list mortality by the Cox proportional hazards model. The waiting list mortality risk of PBC patients was further estimated with adjustment for each scoring system.

Results Of the 1056 patients meeting the inclusion criteria, 743 were not on the list at the end of study period; waiting list mortality was 58.1 % in this group. In multivariate analysis, increasing age and PBC were significantly associated with an increased risk of waiting list mortality. In comparison with patients with hepatitis C virus (HCV) infection, PBC patients were at 79 % increased risk and had a shorter median survival time by approximately 8 months. The relative hazard of PBC patients was statistically significant with adjustment for CTP score and medical point score, which was the priority for ranking candidates in the Japanese allocation system. However, it lost significance with adjustment for MELD score. Stratification by MELD score indicated a comparable waiting list survival time between patients with PBC and HCV.

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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]: $9.57 \times \log_e(\text{creatinine mg/dL}) + 3.78 \times \log_e(\text{bilirubin mg/dL}) + 11.2 \times \log_e(\text{international normalized ratio [INR]}) + 6.43$, 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.

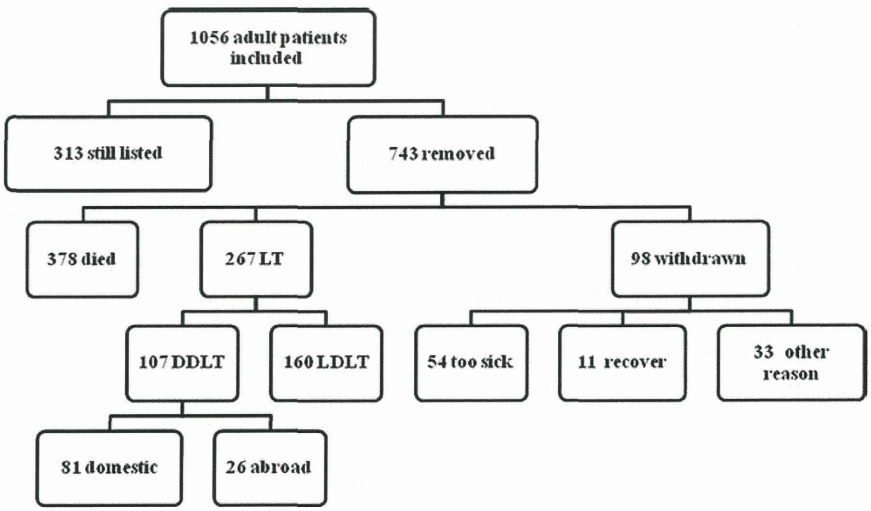

Fig. 1 Flow diagram of patient outcomes. *DDLT* deceased donor liver transplantation, *LDLT* living donor liver transplantation, *LT* liver transplantation

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

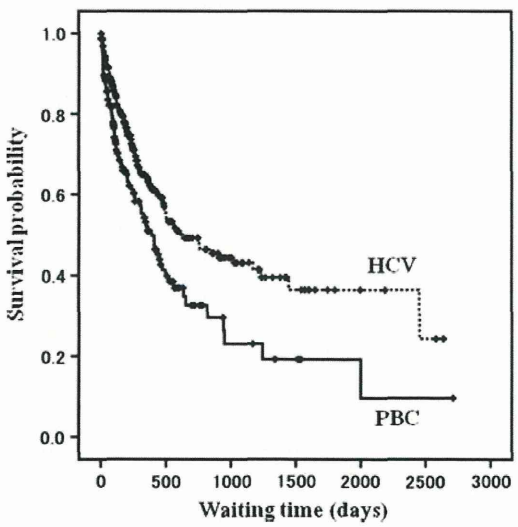

Fig. 2 Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV, $n = 254$) and primary biliary cirrhosis (PBC, $n = 156$)

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

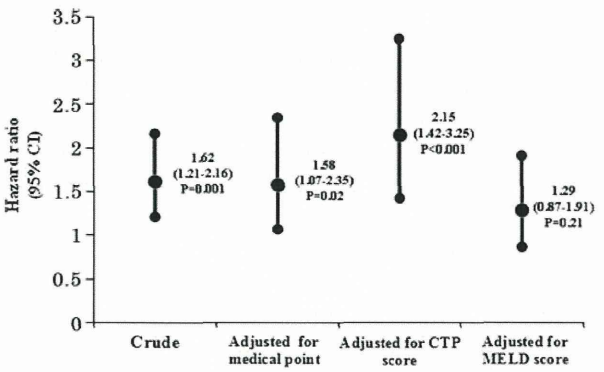

Fig. 3 Adjusted risk of waiting list mortality for patients with primary biliary cirrhosis compared with patients with chronic hepatitis C

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

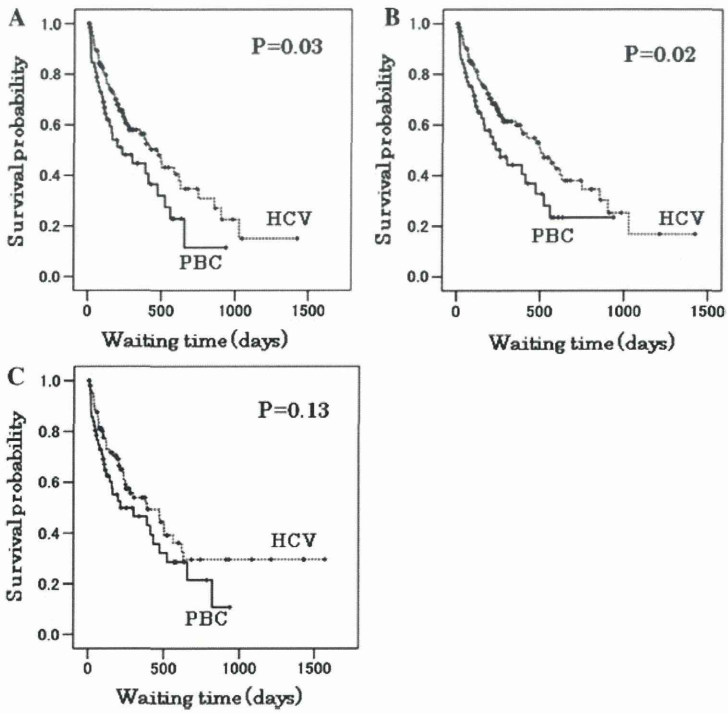

Fig. 4 Kaplan–Meier curves comparing the cumulative waiting list survival probability of patients with chronic hepatitis C (HCV) and primary biliary cirrhosis (PBC). Patients stratified medical point = 6 (**a**), and Child–Turcotte–Pugh score ≥10 (**b**), and Model of End-Stage Liver Disease (MELD) score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

Baseline Serum Cholesterol Is Associated with a Response to Pegylated Interferon Alfa-2b and Ribavirin Therapy for Chronic Hepatitis C Genotype 2

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Background. HCV infection is associated with lipid disorders because this virus utilizes the host lipid metabolism to sustain its life cycle. Several studies have indicated that higher concentrations of serum cholesterol and LDL before treatment are important predictors of higher rates of sustained virological response (SVR). However, most of these studies involved patients infected with HCV genotype 1. Thus, we performed a multi-institutional clinical study to evaluate the impact of lipid profiles on SVR rates in patients with HCV genotype 2. *Methods.* A total of 100 chronic hepatitis C patients with HCV genotype 2 who received peg-IFN alfa-2b and ribavirin therapy were consecutively enrolled. The significance of age, sex, BMI, AST level, ALT level, WBC, hemoglobin, platelet count, gamma-glutamyltransferase, total cholesterol level (TC), LDL level, HCV RNA, and histological evaluation was examined for SVR using logistic regression analysis. *Results.* The 100 patients infected with HCV genotype 2 were divided into 2 groups, an SVR group and a non-SVR group. Characteristics of each group were subsequently compared. There was no significant difference in the level of HCV RNA, BMI, platelet, TG, or stage of fibrosis between the groups. However, there were significant differences in the levels of TC and LDL-C. In multivariate logistic regression analysis using baseline characteristics, high TC level was an independent and significant risk factor (relative risk 18.59, $P = 0.015$) for SVR. *Conclusion.* Baseline serum total cholesterol levels should be considered when assessing the likelihood of sustained treatment response following the course of peg-IFN and ribavirin therapy in patients with chronic HCV genotype 2 infection.

1. Introduction

Hepatitis C virus (HCV) causes acute and chronic hepatitis as well as liver cirrhosis and hepatocellular carcinoma [1]. A single-stranded RNA genome encodes 1 large open reading frame that is processed into at least 10 proteins by host and viral enzymes [2]. Some viral proteins are known to affect the outcome of pegylated interferon (PEG-IFN) and ribavirin combination therapy, which is the current standard for treating chronic hepatitis [3, 4].

HCV infection is associated with lipid disorders because this virus utilizes the host lipid metabolism to sustain its life cycle [5, 6]. Accordingly, understanding lipid metabolism in HCV infection is necessary for developing new strategies for complete eradication of this virus. Characteristic lipid disorders observed in chronic hepatitis C patients include steatosis and hypocholesterolemia, which are primarily caused by abnormal triglyceride (TG) and cholesterol metabolism, respectively [7]. The metabolic pathways of these 2 lipids are closely related to each other.

Several studies have indicated that higher concentrations of serum cholesterol and LDL before treatment are important predictors of high rates of sustained virological response (SVR) [8–10]. However, most of these studies involved patients who were infected with HCV genotype 1. Prognostic factors are likely to differ considerably between genotypes 1 and 2. For example, two studies have shown that total PEG-IFN and ribavirin doses are independent predictive factors of an SVR to the HCV genotype 1, whereas another found that dosages of PEG-IFN and ribavirin on SVR are not related to the genotype 2 [11, 12]. Total dosages of PEG-IFN and ribavirin may similarly influence the SVR to genotypes 1 and 2. Identifying factors involved in the responses of patients infected with HCV genotype 2 to PEG-IFN and ribavirin is important when considering treatment strategies. Fewer patients are infected with HCV genotype 2 than genotype 1. Thus, we performed a multi-institutional clinical study to evaluate the impact of lipid profiles on SVR rates in patients with HCV genotype 2.

2. Patients and Methods

2.1. Patients. A total of 685 patients with chronic hepatitis C diagnosed between 2004 and 2008 in the Nagasaki Association for the Study of Liver Disease (NASLD) were recruited for this study. All patients were included if they were positive for HCV antibodies and serum HCV RNA. One hundred patients with HCV genotype 2 who received pegylated interferon alfa-2b (PEG-INF) and ribavirin therapy were consecutively enrolled. Exclusion criteria were as follows: (1) positive for serum hepatitis B virus surface antigen, (2) abnormal thyroid and kidney functions, (3) decompensated liver disease, (4) presence of human immunodeficiency virus type I infection, and (5) ever received specific antiviral therapy prior to referral.

2.2. Study Protocol. This study is retrospective study. Response to antiviral treatment was assessed in patients based on HCV viremia and aminotransferase levels. Patients treated with a combination of PEG-IFN alfa-2b (product by MSD) and ribavirin received 1.0–1.5 μg/kg and 600–800 mg daily of each drug, respectively. SVR was defined as both normal aminotransferase levels and undetectable serum HCV RNA 24 weeks after the end of antiviral therapy. The remaining patients were considered nonvirus responders (non-SVR).

Fasting serum samples were obtained in the early morning for biochemical analysis. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2). Liver biopsy specimens were fixed in 10% formalin, embedded in paraffin, cut to a thickness of 4 μm, and stained with hematoxylin-eosin and Azan. All liver tissue specimens were evaluated by one pathologist who was unaware of patient clinical conditions. Liver histology was evaluated according to the degree of fibrosis and necroinflammatory activity [13]. The extent of fibrosis (staging) was classified as follows: F1 (periportal expansion), F2 (portoportal septa), F3 (portocentral linkage or bridging fibrosis), and F4 (cirrhosis). Necroinflammatory activity (grading) was classified as follows: A1 (mild), A2 (moderate), and A3 (severe). In order to define the cutoff parameter for total cholesterol level (TC), LDL, and TG for the SVR of PEG-IFN alfa-2b and ribavirin in HCV patients, we used the ROC curve. The area under the curve was 62% (CI 95%: 51%–75%), 72% (CI 95%: 59%–86%), and 61% (CI 95%: 46%–76%), respectively. The ideal cutoff point for the TC, LDL, and TG was calculated to be 177 with sensitivity equal to 58% and specificity equal to 77%, 98 with sensitivity equal to 57% and specificity equal to 77%, and 88 with sensitivity equal to 56% and specificity equal to 67%, respectively.

The protocol was approved by the Ethical Committee of the Nagasaki University School of Medicine.

2.3. Statistical Analysis. Descriptive summaries of study groups are reported as the median (range) and number (%). Data were analyzed using the Mann-Whitney U test for continuous ordinal data, and the chi-square test with Yates' correction and Fisher's exact test were performed for intergroup comparisons to determine the association between 2 qualitative variables. P-values <0.05 were considered statistically significant. Variables achieving statistical significance according to univariate analysis were subsequently included in the multivariate analysis using a logistic regression model and were described as relative risk (RR) with 95% confidence intervals (CI). Coefficients were calculated from the linear discriminating function of the variables. Data analysis was performed using SPSS version 16.0 for Windows.

3. Results

3.1. Patient Clinical Features. Baseline characteristics of the 100 patients infected with HCV genotype 2 are shown in Table 1. There were 54 male (54%) and 46 female (46%) patients, with a median age of 57 years.

The 100 patients infected with HCV genotype 2 were then divided into 2 groups, an SVR group (74 patients) and Non-SVR group (26 patients). Characteristics of each group were subsequently compared (Table 2). There was no

Table 1: Characteristics of 100 studied patients with HCV genotype 2.

All	100	
Age	57.0	(24–76)
Sex (%)		
Male	54	(54)
Female	46	(46)
Height (cm)	162	(138–186)
Weight (kg)	58	(37–87)
BMI (kg/m^2)	22.7	(18.4–30.8)
Clinical finding (%)		
Chronic hepatitis	93	(93)
Cirrhosis	7	(7)
WBC (/μL)	5100	(2100–9730)
Hemoglobin (g/dL)	14.0	(10–16)
Platelet ($10^4/\mu$L)	20.4	(6.9–26.5)
AST (IU/L)	42	(17–157)
ALT (IU/L)	52	(11–280)
TC (mg/dL)	177	(106–269)
<177 mg/dL (%)	50	(50)
≥177 mg/dL (%)	50	(50)
TG (mg/dL)	88	(56–262)
<88 mg/dL (%)	50	(50)
≥88 mg/dL (%)	50	(50)
LDL-C (mg/dL)	98	(30–167)
<98 mg/dL (%)	50	(50)
≥98 mg/dL (%)	50	(50)
HCV RNA (KIU/mL)	1000	(20–40900)
Distribution of stage of fibrosis (%)		
0-1	43	(43)
2	17	(17)
3	11	(11)
4	4	(4)
Unknown	25	(25)
Distribution of grade of inflammation (%)		
0-1	39	(39)
2	34	(34)
3	2	(2)
Unknown	25	(25)
Treatment period (week) (%)		
<24	10	(10)
24	83	(83)
25–48	5	(5)
>48	2	(2)
Therapeutic efficacy (%)		
SVR	74	(74)
Non-SVR	26	(26)

Data are median (range) or frequency (%).

significant difference in the level of HCV RNA, BMI, platelet, TG, or stage of fibrosis between the groups. However, there were significant differences in the level of TC and LDL-C.

3.2. Univariate and Multivariate Analysis of Factors Associated with SVR to Pegylated Interferon Alfa-2b and Ribavirin Therapy. Univariate and multivariate analysis in 100 patients infected with HCV genotype 2 was performed to identify independent factors relevant to an SVR (Table 3). In univariate analysis, the following 2 factors significantly influenced the SVR: TC (≥177 mg/dL; relative risk, 3.77; 95% confidence interval (95% CI), 1.41–10.05; $P = 0.008$) and LDL-C (≥98 mg/dL; relative risk, 4.91; 95% CI, 1.19–20.23; $P = 0.028$). However, in multivariate analysis, TC was the only independent factor for SVR (relative risk, 18.59; 95% CI, 1.78–193.65; $P = 0.015$).

3.3. Association of SVR Rate to Combination Therapy and TC Level. The 100 patients infected with HCV genotype 2 were then divided into 2 groups, a high serum TC level group (≥177 mg/dL) and a low serum TC level group (<177 mg/dL). Characteristics of each group were subsequently compared (Table 4). There was no significant difference in age, the level of ALT, WBC, hemoglobin, platelet, TG, stage of fibrosis or grade of inflammation between the groups. However, there were significant differences in sex, BMI, the level of AST, TG, LDL-C, and HCV RNA.

We examined the differences in the 4 indices related to SVR rate between high serum TC level and low serum TC level in HCV genotype 2 patients (Figure 1). The SVR rate in low serum TC level patients was 62% (31 of 50), whereas 86% of patients (43 of 50) had serum high TC levels. The significantly higher SVR rate of serum high TC level than low serum TC levels was observed in 100 patients infected with HCV genotype 2.

4. Discussion

In this retrospective study, we showed a significant association of treatment response with baseline characteristics of patients infected with HCV genotype 2, including HCV viral load, BMI, and serum cholesterol level. Several baseline predictors for SVR have been identified in earlier studies [14–17]. Notably, among pretreatment features in the present study, serum TC levels appeared to discriminate responders from nonresponders independently of different treatment schedules. The response rate to standard treatment for patients with HCV genotype 2 using a combination of PEG-IFN and ribavirin is approximately 80% and remains a major concern in patient care. Our findings confirm serum high TC level as a good predictor of SVR in genotype 2. In patients with genotype 2, the SVR rate in patients with low serum TC levels was 62%, whereas 86% had high serum TC levels. Serum cholesterol as a predictor of SVR in patients with chronic hepatitis C is in accordance with the results of previous studies [8–10, 18–20]. However, our study design included only patients with HCV genotype 2.

A cutoff value of total cholesterol of 177 mg/dL in this study represented the best value in terms of sensitivity and specificity for SVR. Our cutoff total cholesterol level was lower than other previous studies [8–10, 18–20]. However, American Diabetes Association guidelines suggest that a goal should be a total cholesterol of <160 mg/dL in patient with

Table 2: Factors associated with response to peginterferon alfa-2b and ribavirin therapy.

	SVR	(Range or %)	Non-SVR	(Range or %)	*P* value
Total	74		26		
Age (y.o.)	57	(24–72)	57	(31–78)	NS
Sex (%)					
Male	33	(45)	13	(50)	
Female	41	(55)	13	(50)	NS
BMI (kg/m^2)	23.1	(15.4–30.9)	21.0	(18.4–26.0)	NS
WBC (/μL)	5100	(2100–9730)	5145	(3000–8300)	NS
Hemoglobin (g/dL)	14.1	(10–16)	14.0	(10–16)	NS
Platelet (10^4/μL)	21.7	(6.9–26.5)	11.5	(7.3–21.1)	NS
AST (IU/L)	39	(17–377)	44	(17–140)	NS
ALT (IU/L)	51	(11–751)	53	(14–169)	NS
TC (mg/dL)	183	(106–269)	163	(127–248)	NS
<177 mg/dL (%)	31	(42)	19	(73)	
≥177 mg/dL (%)	43	(58)	7	(27)	0.005
TG (mg/dL)	98	(56–262)	83	(74–176)	NS
<88 mg/dL (%)	33	(44)	17	(67)	
≥88 mg/dL (%)	41	(56)	9	(33)	NS
LDL-C (mg/dL)	109	(30–167)	88	(64–117)	0.015
<98 mg/dL (%)	30	(40)	20	(77)	
≥98 mg/dL (%)	44	(60)	6	(23)	0.020
HCV RNA (KIU/mL)	1000	(20–40900)	1850	(37–24200)	NS
Distribution of stage of fibrosis (%)					
1	31	(42)	12	(46)	
2	14	(19)	3	(12)	
3	6	(8)	5	(19)	
4	3	(4)	1	(4)	
Unknown	20	(27)	5	(19)	NS
Distribution of grade of inflammation (%)					
1	27	(36)	12	(46)	
2	25	(34)	9	(35)	
3	2	(3)	0	(0)	
Unknown	20	(27)	5	(19)	NS

Data are median (range) or frequency (%).

type 2 diabetes who is at low risk [21]. Furthermore, Miller et al. reported that American type 2 diabetic patients had an average cholesterol level of 179 mg/dL [22].

The reason for SVR improvement in patients with elevated serum cholesterol levels is unknown. In patients with chronic hepatitis B and hepatitis C, serum lipid levels have been reported to be correlated with specific cytokines that may have antiviral activity, including tumor necrosis factor-alpha and interleukin-6 [23]. This hyperlipidemia-induced increase in cytokine levels may have a favorable and potentially additive effect on antiviral treatment in patients with chronic hepatitis C. Another proposed mechanism may be related to a possible regulatory effect of cholesterol in HCV binding to cell surface receptors, which in turn may be relevant to viral clearance [24]. The LDL receptor, a membrane glycoprotein, has been shown to be involved in HCV entry into hepatocytes, and data suggest that HCV RNA levels correlate with LDL receptor expression [25, 26]. Elevated serum concentrations of LDL may decrease the number of LDL receptors located on hepatocytes.

Recent studies have shown that single nucleotide polymorphisms located in the gene region encoding interleukin 28b (IL28B) are strongly associated with the response to PEG-IFN and ribavirin therapy [17, 27, 28]. Total cholesterol, LDL cholesterol, and ApoB concentrations are significantly higher in chronic hepatitis C patients carrying a second IL28B major allele (CC in rs 12979860) compared with those possessing minor alleles (CT or TT) [29]. Therefore, the association between serum LDL cholesterol concentration and SVR may be reflected by the underlying link