Prognosis of patients with liver cirrhosis: A multi-center retrospective observational study

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Abstract
Aim: Despite advances in the management of liver diseases and changes in the etiology of cirrhosis, few studies have updated the prognosis of cirrhosis. This study aimed to clarify the recent prognosis of cirrhosis and identify risk factors for death.
Methods: In this retrospective observational study by the Hepatic Disease Network of the National Hospital Organization in Japan, chart reviews were performed to follow patients with cirrhosis beginning in 2011. We conducted Kaplan–Meier survival time analyses stratified by Child–Pugh classification and albumin-bilirubin grade. Cox regression analysis was used to identify risk factors for death.
We identified 444 eligible patients from 25 hospitals, including 303 (68%), 110 (25%), and 31 (7%) patients with Child–Pugh classes A, B, and C, respectively. Hepatitis C virus infection was the cause of cirrhosis for 63% of the patients. The 1-year and 5-year cumulative survival rates of patients with Child–Pugh classes A, B, and C were 90% and 61%, 78% and 42%, and 65% and 25%, respectively. The 1-year and 5-year cumulative survival rates of patients with albumin-bilirubin grades 1, 2, and 3 were 98% and 80%, 91% and 56%, and 58% and 23%, respectively. Cirrhosis classification (Child–Pugh and albumin-bilirubin), age, liver cancer, and untreated esophageal varices were associated with increased hazard of death.

Conclusions: Little improvement was observed in the prognosis of cirrhosis compared with previous reports, and the prognosis of Child–Pugh class C cirrhosis remained poor. Untreated esophageal varices were identified as a risk factor for death.

KEYWORDS
cohort studies, liver cirrhosis, mortality

INTRODUCTION

Cirrhosis is an advanced stage of liver fibrosis caused by chronic liver injuries. Etiologies of cirrhosis include hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcoholic liver diseases, and non-alcoholic steatohepatitis (NASH). Portal hypertension and impaired hepatic function in cirrhosis cause complications including variceal hemorrhage, infection, and encephalopathy.1,2

Previous studies have shown that the prognosis of cirrhosis varies widely depending on the condition’s clinical stage. The Child–Pugh classification3,4 is one of the most widely used classification systems to predict the prognosis of patients with cirrhosis. In a systematic review of studies published from 1983 to 2005, the 1-year survival rates of patients with Child–Pugh classes A, B, and C were 95%, 80%, and 45%, respectively.5 Recently, the albumin-bilirubin (ALBI) grade has been proposed as a simple and objective alternative to the Child–Pugh classification.6 Several studies have reported the usefulness of the ALBI grade.7–9

The etiology of cirrhosis is changing, with a decreasing prevalence of cases associated with HCV and an increasing prevalence of cases associated with alcohol and NASH.10 Additionally, there have been advances in the diagnosis and management of patients with liver diseases, including the approval of nucleoside analogues for treating HBV infection.11 An administrative claims database study of hospitalized patients has reported the recent prognosis of patients with cirrhosis.12 However, few clinical studies have updated this prognosis.9 Furthermore, no recent studies have examined independent prognostic factors in addition to the stage of cirrhosis.

The National Hospital Organization (NHO) is an independent administrative agency in Japan that manages hospitals nationwide. The Hepatic Disease Network is a clinical study group of the NHO. Using data on patients treated in hospitals participating in this study group, we conducted a multi-center retrospective observational study to clarify the recent prognosis of patients with cirrhosis and identify risk factors for death.

METHODS

Study setting and overview

The NHO was established in 2004 to take over the management of the national hospitals in Japan. As of 2018, 142 hospitals nationwide were run by the NHO. All NHO hospitals provide administrative data to the Medical Information Analysis (MIA) databank, which is managed at the NHO Headquarters. The present study was conducted in 2019 at the NHO Headquarters and at NHO hospitals participating in the Hepatic Disease Network. We used the MIA databank to identify patients meeting the selection criteria, and researchers in the participating hospitals conducted chart abstraction. This study conforms to the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of the NHO Nagasaki Medical Center. Because of the retrospective and non-invasive nature of the study, the need for informed consent was waived.

Patients

Using the MIA databank, we identified patients with chronic liver disease who were treated in the 36 participating hospitals from April 2011 to March 2012. The inclusion criteria were as follows: age ≥20 years, a confirmed record of diagnosis of chronic liver disease (as presented in Table S1), two or more hospital visits from April 2011 to
March 2012, and two or more imaging tests by ultrasonography, computed tomography, or magnetic resonance imaging from April 2011 to March 2012. Day of patient registration was defined as the day that medical care started for the diagnosis of chronic liver disease, as recorded in the claims data, or the earliest day that imaging was conducted—whichever occurred later within the April 2011–March 2012 period. We excluded patients who did not visit the same hospital again within 1 year after the registration day and those who were followed for less than 6 months after the registration day.

From the cohort of eligible patients, we randomly selected patients to be reviewed at each participating hospital. To minimize the load on the researchers at each hospital, we selected the sampling proportion of 10% or 20%, depending on the number of patients at each hospital. The type of chronic liver disease (cirrhosis, chronic hepatitis without cirrhosis, or other) was confirmed by the researchers at the participating hospitals. For this study, we analyzed patients who were confirmed as having cirrhosis at the time of registration. In accordance with published guidelines,13,14 cirrhosis was determined by a combination of the following data extracted from patients’ charts: patient characteristics, physical findings, serum biomarker concentrations, imaging findings (ultrasonography, computed tomography, and magnetic resonance imaging), upper gastrointestinal endoscopy, and liver biopsy.

Variables

Data on each patient's age and sex were extracted from the MIA databank. The following information at the time of registration was obtained by chart review: etiology of cirrhosis (HCV, HBV, alcohol, primary biliary cholangitis, autoimmune hepatitis, metabolic causes including NASH, other, or unknown), treatment status of HCV and HBV infections, Child–Pugh class, presence and stage of liver cancer, status of esophageal varices (none, untreated, history of preventive endoscopic variceal ligation, history of bleeding, and no screening), alcohol consumption, clinical conditions (ascites and encephalopathy), and laboratory data (total bilirubin, albumin, prothrombin time, platelet count, sodium, potassium, chloride, blood urea nitrogen, creatinine, and alpha-fetoprotein). HCV and HBV infections were determined by positive HCV antibody and HBs antigen, respectively. We calculated the ALBI score as follows: ALBI score = 0.66 × log$_{10}$ (bilirubin [μmol/L]) – 0.085 × albumin (g/L). The ALBI score was categorized into three grades: grade 1, ≤−2.60; grade 2, >−2.60, ≤−1.39; and grade 3, >−1.39.6 The latest date of follow-up and status (alive or dead) at the end of follow-up were also obtained by chart review.

Statistical analysis

Analyses were conducted for patients with data on Child–Pugh class, etiology, outcome, and follow-up period. In patients with albumin and bilirubin data available, we compared the ALBI grade with the Child–Pugh class. We conducted survival time analyses using the Kaplan–Meier method stratified by the Child–Pugh class, and we calculated the cumulative survival rates at 1, 2, 3, and 5 years. The study selection criteria required that patients be observed alive for at least 6 months. Because this requirement could bias the survival time, we estimated the mortality from 0 to 6 months using the mortality from 6 to 12 months. Two survival time analyses—one stratified by ALBI grade and the other stratified by the etiology of cirrhosis—were conducted in the same manner. We also categorized patients using a combination of Child–Pugh class and ALBI grade (nine possible groups) and performed survival time analysis. The log-rank test was used to compare outcomes between patients with different ALBI grades within the same Child–Pugh class and between patients with different Child–Pugh within the same ALBI grade.

We performed multivariable Cox regression analysis to identify factors associated with death. The following variables at the time of registration were used as predictors: age, sex, Child–Pugh class, etiology, status of liver cancer, status of esophageal varices, and alcohol consumption. ALBI grade was not included in the model because of collinearity with Child–Pugh class. Clinical conditions and laboratory data were not included because some of these factors are represented in the Child–Pugh class and because others had various numbers of patients with missing data.

We conducted four additional analyses. First, we ran multivariable Cox regression analysis using the ALBI grade instead of the Child–Pugh. Second, we confirmed the survival time of the patients who were excluded from the main analysis because of missing data on Child–Pugh class or etiology of cirrhosis. Third, we conducted a sensitivity analysis taking into account the different sampling proportions across hospitals. First, using the chi-squared test, we compared baseline characteristics between the patients from hospitals with a 10% sampling rate and the patients from hospitals with a 20% sampling rate. Then, the main analyses were conducted after applying a twofold weight for the patients from hospitals with 10% sampling. Finally, we conducted a sensitivity analysis estimating the mortality from 0 to 6 months as twice the mortality from 6 to 12 months.

p values < 0.05 were considered statistically significant. Statistical analyses were conducted using Stata MP, version 15.1 (Stata-Corp, College Station).

RESULTS

The flow of patient selection is presented in Figure 1. Data extraction from the MIA databank identified 15,992 eligible patients from 33 hospitals. We conducted 10% sampling for nine hospitals and 20% sampling for 24 hospitals, yielding a total of 2340 patients for chart review. Review results were retrieved for 1809 patients from 25 hospitals (response rate: 77% at patient level and 76% at hospital level). Overall, 563 patients were confirmed as having cirrhosis, and 444 patients from 25 hospitals were included in the main analysis.
Baseline patient characteristics are presented in Table 1, and baseline clinical and laboratory findings are presented in Table 2. The mean age was 69 years (standard deviation = 10.0 years), and 59% of the patients in the sample were male. Overall, there were 303 (68%), 110 (25%), and 31 (7%) patients with Child–Pugh classes A, B, and C, respectively. HCV was the predominant cause of cirrhosis. Among the 280 patients with HCV, 187 (66%) were untreated, 28 (10%) had received treatment and had a sustained viral response, and 42 (15%) had received treatment but did not have a sustained viral response. Among the 58 patients with HBV, 36 (62%) had received treatment and 16 (28%) had not. In the 436 patients with data on both albumin and total bilirubin, the ALBI grade was compared with the Child–Pugh class (Table 3). Among the 296 patients with Child–Pugh class A cirrhosis, 74 (25%) and 215 (73%) were classified as ALBI grades 1 and 2, respectively. Overall, the median period of observation was 49 months, and 203 patients (46%) died. The results of the survival time analyses with stratification are presented in Table 4, and Figures 2 and 3 show the survival time curves stratified by Child–Pugh class and by ALBI grade, respectively. The 1-year and 5-year cumulative survival rates for patients with Child–Pugh classes A, B, and C were 90% and 61%, 78% and 42%, and 65% and 25%, respectively. In patients with hepatitis C, the 1-year and 5-year cumulative survival rates were 85% and 52%, respectively. Figure 4 shows survival time curves stratified by a combination of Child–Pugh class and ALBI grade. Differences in prognosis between patients with different ALBI grades were significant for patients with Child–Pugh classes A and B (p < 0.001, p = 0.044, and p = 0.076 in patients with Child–Pugh classes A, B, and C, respectively). In contrast, among patients with the same ALBI grade, there were no significant differences in prognosis between different Child–Pugh classes (p = 0.697, p = 0.826, and p = 0.225 in patients with ALBI grades 1, 2, and 3, respectively). The result of multivariable Cox regression analysis is presented in Table 5. In addition to Child–Pugh class, age, presence of liver cancer, and untreated esophageal varices were associated with increased hazard of death. Sex, etiology of cirrhosis, and alcohol consumption were not associated with increased hazard of death. The result of an analysis using ALBI grade is presented in Table S2. In addition to the factors found to be significant in the main analysis, metabolic cause and history of esophageal varix bleeding were associated with increased hazard of death. A total of 107 patients were excluded from the main analysis because of missing data on Child–Pugh class or etiology of cirrhosis. The 1-year and 5-year cumulative survival rates of these patients were 94% and 75%, respectively. These rates were marginally better than the survival rates of patients with Child–Pugh class A, but the difference was not statistically significant by log-rank test (p = 0.0502). The comparison of baseline characteristics between the 96 patients from five hospitals with 10% sampling and the 348 patients from 20 hospitals with 20% sampling is presented in Table S3. Statistically significant differences were observed in etiology, liver cancer, esophageal varices, and alcohol consumption. After weighting by sampling proportion, the mean age was 71 years (standard deviation = 10.0 years), and 59% of the patients in the sample were male.

**Figure 1** Selection of patients with cirrhosis observed in hospitals participating in the Hepatic Disease Network of the National Hospital Organization. The total number of patients with each missing value exceeds the total number of excluded patients because some patients had multiple missing values. MIA, Medical Information Analysis.
The results of the survival time analyses estimating the mortality from 0 to 6 months as twice the mortality from 6 to 12 months are presented in Table S6. The 1-year and 5-year cumulative survival rates for patients with Child–Pugh classes A, B, and C were 85% and 58%, 67% and 37%, and 49% and 19%, respectively.

**DISCUSSION**

Using charts from multiple hospitals participating in the Hepatic Disease Network of the NHO, we conducted a retrospective observational study to describe the prognosis of patients with cirrhosis. Follow-up for the 444 patients beginning in 2011 showed 1-year and 5-year cumulative survival rates of 90% and 83%, 78% and 65%, and 65% and 47%, respectively. Multivariable analysis identified untreated esophageal varices as an independent risk factor for death.

In our cohort of patients registered in 2011 with known etiology, the majority had cirrhosis caused by HCV (63%), followed by alcohol (16%) and HBV (13%). According to a previous nationwide survey in Japan, the cause of cirrhosis diagnosed in 2011–2013 was HCV in 45% of cases, alcohol in 24% of cases, and HBV in 10% of cases, with cryptogenic cirrhosis accounting for 7.5% of cases. Compared with this previous survey, our cohort included slightly more patients with viral cirrhosis. The distributions of age and sex in our sample were comparable to those reported from the previous survey. In the present study, the percentage of patients who had been treated for viral infections was 62% for those with HBV and 25% for those with HCV. In Japan, the nucleoside analogues lamivudine, adefovir, and entecavir were approved for treating HBV in 2000, 2004, and 2006, respectively. However, pegylated interferon with ribavirin was the main HCV treatment until the approval of interferon-free therapy with direct-acting antivirals in 2014. The treatment status of our cohort reflected these situations during the study period.

Patients who were eligible for this study were randomly selected from cases identified using the MIA databank. The sampling rate differed between large-volume (10%) and small-volume (20%) hospitals. However, the key background characteristics were similar between patients from hospitals with a 10% sampling rate and patients from hospitals with a 20% sampling rate. Additionally, the results of the sensitivity analysis with weighing were identical to those of the main analysis. Therefore, the sampling method in this study had a small effect on patient representativeness.

We found that the 1-year and 2-year cumulative survival rates of patients with Child–Pugh classes A, B, and C were 90% and 83%, 78% and 65%, and 65% and 47%, respectively. These numbers were mostly within the interquartile range of survival rates reported in a previous systematic review, although patients with class C cirrhosis had a

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| Characteristic       | n   | %   |
|----------------------|-----|-----|
| **Age, years**       |     |     |
| <60                  | 75  | 17  |
| 60–69                | 128 | 29  |
| 70–79                | 177 | 40  |
| ≥80                  | 64  | 14  |
| **Sex**              |     |     |
| Male                 | 262 | 59  |
| Female               | 182 | 41  |
| **Child–Pugh class** |     |     |
| Class A              | 303 | 68  |
| Class B              | 110 | 25  |
| Class C              | 31  | 7   |
| **Albumin-bilirubin grade** | | |
| Grade 1              | 76  | 17  |
| Grade 2              | 286 | 64  |
| Grade 3              | 74  | 17  |
| Missing              | 8   | 2   |
| **Etiology of cirrhosis** | | |
| Hepatitis C          | 280 | 63  |
| Hepatitis B          | 58  | 13  |
| Alcohol              | 70  | 16  |
| Primary biliary cholangitis | 7 | 2 |
| Autoimmune hepatitis | 9   | 2   |
| Metabolic            | 20  | 5   |
| **Liver cancer**     |     |     |
| None                 | 225 | 51  |
| Stage I or II cancer | 141 | 32  |
| Stage III or IV cancer | 58 | 13 |
| **Cancer with missing data on stage** | | |
| Cancer with missing data on stage | 10 | 2 |
| Missing              | 10  | 2   |
| **Status of esophageal varices** | | |
| None                 | 170 | 38  |
| Untreated            | 104 | 23  |
| Post-EVL             | 50  | 11  |
| History of bleeding  | 25  | 6   |
| No screening         | 95  | 21  |
| **Alcohol consumption** | | |
| No                   | 349 | 79  |
| Yes                  | 83  | 19  |
| Missing              | 12  | 3   |

Abbreviation: EVL, endoscopic variceal ligation.
Thus, we conclude that the prognosis of patients with cirrhosis at each stage has remained mostly unchanged, with the possibility of a slight improvement among patients with Child–Pugh class C cirrhosis. Interferon-free therapy with direct-acting antivirals was approved for HCV infection in 2014, but was not approved for decompensated cirrhosis until 2019. Similarly, although studies have reported the effectiveness of rifaximin for hepatic encephalopathy, its approval in 2016 would have had little impact in our cohort. Branched-chain amino acid infusion is reported to improve short-term prognoses of patients with hepatic encephalopathy. Also, zinc and carnitine supplementations can reportedly achieve improvement in symptoms and laboratory findings of hepatic encephalopathy. However, thus far there is no conclusive evidence for the effect of these treatments on long-term prognosis. Advances in screening and antiviral therapy, including nucleoside analogues for HBV infection, may have been effective in preventing cirrhosis or slowing progression. However, these advances may not have affected the prognoses of patients who already had Child–Pugh class C cirrhosis in 2011. Further research on treatment for cirrhosis is necessary.

A recent study using an administrative claims database also reported the prognosis of patients with cirrhosis in Japan. The survival rates reported in this previous study were similar to those found in the present study for Child–Pugh classes A and B. However, the prognosis was worse in the previous study for Child–Pugh class C. This difference may be caused by the studies’ different inclusion criteria: an episode of hospitalization for cirrhosis was the point of cohort entry in the previous study, whereas outpatients were included in our study. The present study was relatively small in scale. However, the strength of our study lies in the thorough chart review by experts in the participating hospitals. The proportion of patients with missing Child–Pugh classification or unknown etiology was small, and the patients’ background characteristics were in line with results from the nationwide survey. Additionally, we were able to follow the patients for long time period (median = 49 months). Most previous studies have reported the prognosis of cirrhosis up to 2 or 3 years. Our study extended this time frame, reporting 5-year cumulative survival rates.

In addition to the Child–Pugh classification, we grouped patients on the basis of the newly proposed ALBI grade. Unlike the Child–Pugh classification, ALBI grade does not require subjective decisions and is easily calculable from laboratory data. To our knowledge, this is the first study to report the prognosis of patients with different types of cirrhosis using the ALBI grade. The 5-year cumulative survival rates were 80%, 56%, and 23% in patients with ALBI grades 1, 2, and 3, respectively. A previous single-center study of patients with HBV-related hepatocellular carcinoma reported 5-year cumulative survival rates of 78%, 30%, and 3% in patients with ALBI grades 1, 2, and 3, respectively. The prognosis in our cohort, which included patients without liver cancer, was unsurprisingly better than that reported in the previous study. However, ALBI grade was found to be similarly effective for predicting prognosis. As shown in Figure 4, ALBI grade further differentiated the prognoses of patients with Child–Pugh classes A and B. In contrast, patients with different Child–Pugh classes had similar prognoses if they were categorized into the same ALBI grade. These findings support the utility of ALBI grade.

| Variable         | Statistic     | Number of patients with data |
|------------------|---------------|------------------------------|
| Clinical conditions<sup>a</sup> |               |                              |
| Ascites          | 76 (18)       | 426                          |
| Encephalopathy   | 26 (6)        | 422                          |
| Laboratory data<sup>b</sup> |               |                              |
| Total bilirubin, mg/dL | 1.0 (0.7–1.5) | 441                          |
| Albumin, g/dL    | 3.6 (3.2–4.0) | 439                          |
| Prothrombin time, % | 80 (67–92)    | 404                          |
| Platelet count, 10<sup>4</sup>/μL | 9.4 (6.9–13.2) | 442                          |
| Sodium, mEq/L    | 140 (138–141) | 401                          |
| Potassium, mEq/L | 4.2 (3.9–4.4) | 406                          |
| Chloride, mEq/L  | 105 (103–107) | 391                          |
| Blood urea nitrogen, mg/dL | 15 (12–20)     | 420                          |
| Creatinine, mg/dL | 0.73 (0.61–0.90) | 437                      |
| Alpha-fetoprotein, ng/mL | 8.5 (4.1–26.2) | 400                          |

<sup>a</sup>Data shown as n (%).

<sup>b</sup>Data shown as median (interquartile range).

| Child–Pugh classification | Albumin-bilirubin grade | Grade 1 | Grade 2 | Grade 3 | Total |
|---------------------------|-------------------------|---------|---------|---------|-------|
| Class A                   | 74 (25)                 | 215 (73)| 7 (2)   | 296    |
| Class B                   | 2 (2)                   | 65 (60)| 42 (39) | 109    |
| Class C                   | 0 (0)                   | 6 (19)| 25 (81) | 31     |
| Total                     | 76 (17)                 | 286 (66)| 74 (17)| 436    |

Note: Data shown as n (%).

| Variable | Statistic     | Number of patients with data |
|----------|---------------|------------------------------|
| Grade 1  |               |                              |
| Grade 2  |               |                              |
| Grade 3  |               |                              |

Although approximately 20 years have passed since the previous reports, the prognosis remains poor for patients with Child–Pugh class C cirrhosis. Better prognosis in our study, some caution is required when comparing these results, however, because the inclusion criteria of our study required that patients be observed alive for at least 6 months. The main analysis estimated the mortality during this period using the mortality from 6–12 months. The sensitivity analysis that doubled the estimated mortality rate during the 0–6-month period resulted in a cumulative survival rate for patients with Child–Pugh class C that was similar to that reported in the previous review. Thus, we conclude that the prognosis of patients with cirrhosis at each stage has remained mostly unchanged, with the possibility of a slight improvement among patients with Child–Pugh class C cirrhosis. 

Table of Baseline clinical and laboratory findings of 444 patients with cirrhosis identified in 2011.

| Variable | Statistic | Number of patients with data |
|----------|-----------|------------------------------|
| Clinical conditions<sup>a</sup> | | |
| Ascites | 76 (18) | 426 |
| Encephalopathy | 26 (6) | 422 |
| Laboratory data<sup>b</sup> | | |
| Total bilirubin, mg/dL | 1.0 (0.7–1.5) | 441 |
| Albumin, g/dL | 3.6 (3.2–4.0) | 439 |
| Prothrombin time, % | 80 (67–92) | 404 |
| Platelet count, 10<sup>4</sup>/μL | 9.4 (6.9–13.2) | 442 |
| Sodium, mEq/L | 140 (138–141) | 401 |
| Potassium, mEq/L | 4.2 (3.9–4.4) | 406 |
| Chloride, mEq/L | 105 (103–107) | 391 |
| Blood urea nitrogen, mg/dL | 15 (12–20) | 420 |
| Creatinine, mg/dL | 0.73 (0.61–0.90) | 437 |
| Alpha-fetoprotein, ng/mL | 8.5 (4.1–26.2) | 400 |

<sup>a</sup>Data shown as n (%).

<sup>b</sup>Data shown as median (interquartile range).

Table of Comparison of Child–Pugh classification and albumin-bilirubin grade in 436 patients with cirrhosis.

| Child–Pugh classification | Albumin-bilirubin grade | Grade 1 | Grade 2 | Grade 3 | Total |
|---------------------------|-------------------------|---------|---------|---------|-------|
| Class A                   | 74 (25)                 | 215 (73)| 7 (2)   | 296    |
| Class B                   | 2 (2)                   | 65 (60)| 42 (39) | 109    |
| Class C                   | 0 (0)                   | 6 (19)| 25 (81) | 31     |
| Total                     | 76 (17)                 | 286 (66)| 74 (17)| 436    |

Note: Data shown as n (%).
We conducted multivariable Cox regression analysis to identify the risk factors for death other than Child–Pugh class. As expected, age and presence of liver cancer were associated with death. The etiology of cirrhosis was not associated with death. However, the number of patients with each etiology was small in the present study. Thus, further large-scale studies may be required. A notable finding

### TABLE 4 Results of survival time analysis of patients with cirrhosis

| Group of patients       | N  | Deaths | Median observation length, months | Cumulative survival rate, % (95% confidence interval) |
|-------------------------|----|--------|----------------------------------|------------------------------------------------------|
|                         |    |        |                                  | 1 year      | 2 years | 3 years | 5 years      |
| All                     | 444| 203    | 49                               | 85.1 (82.4–87.1) | 75.3 (71.5–78.4) | 67.4 (63.2–71.1) | 53.5 (48.7–58.0) |
| Child–Pugh class        |    |        |                                  |            |         |         |               |
| Class A                 | 303| 120    | 56                               | 90.2 (87.2–92.1) | 82.8 (78.5–86.0) | 74.4 (69.3–78.6) | 61.1 (55.2–66.4) |
| Class B                 | 110| 62     | 43.5                             | 77.6 (70.8–81.8) | 64.7 (56.3–71.2) | 58.5 (49.7–65.7) | 42.4 (33.2–50.9) |
| Class C                 | 31 | 21     | 26                               | 65.0 (49.9–73.2) | 46.6 (31.1–58.8) | 37.3 (22.3–50.8) | 24.9 (11.1–40.2) |
| Albumin-bilirubin grade |    |        |                                  |            |         |         |               |
| Grade 1                 | 76 | 19     | 80.5                             | 97.7 (90.1–98.8) | 92.0 (83.1–96.0) | 87.6 (77.5–93.1) | 79.6 (68.0–87.3) |
| Grade 2                 | 286| 131    | 50                               | 90.9 (87.8–92.8) | 82.3 (77.8–85.8) | 73.1 (67.7–77.6) | 56.3 (50.1–62.0) |
| Grade 3                 | 74 | 51     | 22.5                             | 58.4 (49.4–64.8) | 40.5 (31.1–48.9) | 33.2 (24.0–42.0) | 23.1 (14.6–32.3) |
| Etiology of cirrhosis   |    |        |                                  |            |         |         |               |
| Hepatitis C             | 280| 129    | 45.5                             | 85.4 (81.8–87.8) | 74.7 (69.8–78.6) | 67.0 (61.5–71.7) | 51.7 (45.6–57.4) |
| Hepatitis B             | 58 | 22     | 81                               | 89.8 (80.1–93.1) | 84.6 (73.7–90.1) | 75.8 (63.3–83.8) | 64.4 (50.8–74.7) |
| Alcohol                 | 70 | 33     | 53                               | 78.3 (69.2–83.2) | 68.7 (58.1–76.0) | 61.4 (50.1–70.0) | 56.6 (44.9–65.9) |
| Primary biliary cholangitis | 7  | 3     | 43                               | 100 (100–100) | 85.7 (33.4–97.9) | 71.4 (25.8–92.0) | 53.6 (13.2–82.5) |
| Autoimmune hepatitis    | 9  | 4      | 57                               | 79.0 (38.5–87.4) | 79.0 (38.5–87.4) | 79.0 (38.5–87.4) | 47.4 (15.7–70.7) |
| Metabolic               | 20 | 12     | 36                               | 90.3 (66.0–94.3) | 73.9 (48.5–86.5) | 61.6 (35.6–78.5) | 32.9 (11.5–55.7) |

**FIGURE 2** Kaplan–Meier survival time curves of 444 patients with cirrhosis stratified by Child–Pugh class
**Figure 3** Kaplan–Meier survival time curves of 436 patients with cirrhosis stratified by ALBI grade. ALBI, albumin-bilirubin.

**Figure 4** Kaplan–Meier survival time curves of 436 patients with cirrhosis stratified by Child–Pugh class and ALBI grade. ALBI, albumin-bilirubin; CP, Child–Pugh.
TABLE 5 Result of multivariable Cox regression analysis for death in 444 patients with cirrhosis

| Variable                        | Hazard ratio | 95% confidence interval | p value |
|--------------------------------|--------------|--------------------------|---------|
| Age, years                     | 1.05         | 1.03–1.07                | <0.001  |
| Sex                            |              |                          |         |
| Male                           | Reference    |                          |         |
| Female                         | 0.79         | 0.58–1.07                | 0.125   |
| Child–Pugh class               |              |                          |         |
| Class A                        | Reference    |                          |         |
| Class B                        | 1.66         | 1.18–2.33                | 0.004   |
| Class C                        | 4.95         | 2.93–8.36                | <0.001  |
| Etiology of cirrhosis          |              |                          |         |
| Hepatitis C                    | Reference    |                          |         |
| Hepatitis B                    | 0.98         | 0.60–1.61                | 0.942   |
| Alcohol                        | 1.11         | 0.70–1.76                | 0.671   |
| Primary biliary cholangitis    | 0.76         | 0.23–2.48                | 0.651   |
| Autoimmune hepatitis           | 0.71         | 0.25–2.01                | 0.521   |
| Metabolic                      | 1.45         | 0.78–2.68                | 0.240   |
| Liver cancer                   |              |                          |         |
| None                           | Reference    |                          |         |
| Stage I or II cancer           | 1.71         | 1.22–2.40                | 0.002   |
| Stage III or IV cancer         | 4.00         | 2.65–6.04                | <0.001  |
| Cancer with missing data on stage| 1.33       | 0.52–3.37                | 0.553   |
| Missing                        | 1.83         | 0.63–5.37                | 0.270   |
| Status of esophageal varices    |              |                          |         |
| None                           | Reference    |                          |         |
| Untreated                      | 1.62         | 1.11–2.38                | 0.013   |
| Post-EVL                       | 1.22         | 0.73–2.04                | 0.454   |
| History of bleeding            | 1.14         | 0.61–2.15                | 0.678   |
| No screening                   | 1.26         | 0.84–1.89                | 0.254   |
| Alcohol consumption            |              |                          |         |
| No                             | Reference    |                          |         |
| Yes                            | 1.20         | 0.81–1.79                | 0.367   |
| Missing                        | 0.94         | 0.38–2.34                | 0.902   |

Abbreviation: EVL, endoscopic variceal ligation.

was that, after controlling for other characteristics, patients with untreated esophageal varices had an increased risk of death compared with those without esophageal varices. Current guidelines recommend preventive treatment of esophageal varices depending on the form and the red color sign. Assuming that the physicians followed these guidelines, the varices that remained untreated on the basis of the current criteria may have been associated with mortality. Endoscopic findings, screening frequency, and cause of death were not evaluated in the present study. More detailed research may lead to the refinement of the recommendations and better prognosis of patients.

Several limitations of this study must be acknowledged. First, this was a retrospective study using preexisting patient charts. The quality of data is dependent on the quality of recording at the participating hospitals. Second, follow-up results were only available from the hospital at which the patient was originally registered. Although some charts included notifications of death from other institutions, patients could not be systematically followed when they
were transferred to another hospital or moved to another area. Nevertheless, we were able to follow the patients for long time period. Third, patients were recruited into the cohort as of 2011. Although inception cohorts are ideal, the chronic and less symptomatic nature of cirrhosis make this approach difficult. Previous studies have also used alternative recruitment methods. Fourth, in this study we evaluated all-cause mortality and had limited information about the cause of death and occurrence of liver transplantation. Fifth, because we conducted random sampling, there were few patients in some subgroups. Further large-scale studies may be necessary to confirm our findings. Finally, this study was conducted in hospitals participating in the Hepatic Disease Network. Patient characteristics and quality of care at these referral centers may not be fully representative of hospitals in Japan.

In conclusion, in comparison with previous reports, little improvement in the prognosis of patients with cirrhosis was observed in this multicenter retrospective observational study with a long follow-up period beginning in 2011. Child-Pugh class C cirrhosis remained a condition with poor prognosis. The study also identified untreated esophageal varices as a risk factor for death and confirmed the utility of ALBI grade for predicting the prognosis of cirrhosis.

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CONFLICT OF INTEREST

All other authors declare that they have no potential conflict of interest.

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