Real-world hospital mortality of liver cirrhosis inpatients in Japan: a large-scale cohort study using a medical claims database

Prognosis of liver cirrhosis

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Abstract

Aim: Prognosis of liver cirrhosis patients is poor when ascites is present and liver function is impaired, but such up-to-date information from a large-scale, real-world setting is limited in Japan. We aimed to investigate the hospital mortality of Japanese liver cirrhosis inpatients.

Methods: This retrospective cohort study included data on liver cirrhosis inpatients between January 2011 and September 2018 extracted from an administrative claims database. The outcome was in-hospital mortality. The 1- and 3-year cumulative survival rates were examined for liver cirrhosis etiology, Child–Pugh classification, or ascites presence/absence using Kaplan–Meier analysis. The survival up to 1 year for tolvaptan prescription/nonprescription was examined.

Results: We analyzed the data of 57 769 inpatients. Survival rates did not substantially differ among etiologies, with a better prognosis for alcohol etiology and poorer prognosis for hepatitis C virus. According to the Child–Pugh classification, the 1- and 3-year survival rates were 90.2% and 75.3% for grade A, 73.5% and 53.9% for grade B, and 41.9% and 28.9% for grade C, respectively. Patients without ascites had a higher survival rate (83.2% and 67.0% at 1 and 3 years, respectively) than those with ascites (51.9% and 36.3%, respectively). Based on examining matched patients with ascites using a propensity score, prognosis was poor in general but was better at 6 months (58.1%) or similar at 1 year (47.1%) in patients prescribed tolvaptan compared to those not prescribed tolvaptan (54.8% and 47.5%, respectively).

Conclusions: Poorer prognosis was suggested in inpatients with cirrhosis who had a worse Child–Pugh grade and ascites.

Keywords
Child–Pugh classification, etiology, liver cirrhosis, survival, tolvaptan
INTRODUCTION

Liver cirrhosis is an irreversible end-stage liver disease. There are various liver cirrhosis etiologies, including viral hepatitis B and C, and alcoholic and nonalcoholic steatohepatitis (NASH). In previous decades, Japanese studies revealed a decreasing prevalence of liver cirrhosis associated with hepatitis C and an increasing prevalence associated with alcohol and NASH. These trends could be largely due to the development of potent antiviral therapies and changes in lifestyle.

Ascites is the most common comorbidity in liver cirrhosis patients. The results of previous studies showed that approximately 40%–67% of patients had ascites. Among Japanese inpatients, 50.9% had ascites, and the percentage was the highest in patients with alcoholic cirrhosis (60.1%). Ascites development is associated with poor quality of life and poor prognosis. One-year survival probability in liver cirrhosis patients with ascites is approximately 45%–85%, and 5-year survival probability is as low as 34%–57%. However, these studies were undertaken over a decade ago or at a single institution in Japan, and up-to-date reports on prognosis in clinical settings are of benefit to understand clinical practice.

Tolvaptan (Otsuka Pharmaceutical Co., Ltd.) is a selective vasopressin V2-receptor antagonist that has an aquaretic effect, promoting excess water excretion without increasing electrolyte excretion. In September 2013, tolvaptan gained its first approval in Japan for treating fluid retention in patients with hepatic cirrhosis when treatment with other diuretics, including loop diuretics, is not sufficiently effective. In the Evidence-based Clinical Practice Guidelines for Liver Cirrhosis 2015, concomitant tolvaptan therapy with spironolactone and furosemide was recommended for inpatients with nonresponsive ascites or massive-volume ascites. Favorable efficacy and safety profiles of tolvaptan in the treatment of ascites have been previously reported among liver cirrhosis patients. However, its effect on prognosis in liver cirrhosis patients with ascites is not sufficiently elucidated.

The Child–Pugh classification is a common liver cirrhosis severity system used in both clinical research and clinical practice. This classification, originally developed as a new liver function index in patients with cirrhosis, is one of the most commonly used classifications, and according to previous systematic reviews, is a robust tool for predicting mortality in liver cirrhosis patients. There are, however, few reports on the prognosis of Japanese liver cirrhosis patients by liver cirrhosis etiology and Child–Pugh classification.

This study, therefore, aimed to investigate the real-world hospital mortality of liver cirrhosis inpatients, using a large-scale hospital-based administrative claims database across Japan. We examined the mortality of inpatients stratified by liver cirrhosis etiology, Child–Pugh classification, and ascites. Moreover, mortality was further examined in liver cirrhosis inpatients with ascites who were treated with and without tolvaptan, using a propensity score matching.

METHODS

Study design and data source

This retrospective cohort study was undertaken using a hospital-based administrative claims database constructed by the Medical Data Vision Co., Ltd (MDV). The MDV database is the largest of its kind in Japan. It contains information on demographics (e.g., age and sex), and medical records including diagnosis records, medical procedures, prescriptions, inpatient or outpatient status, and laboratory data, from 23.98 million people in 372 acute care hospitals that adopted the diagnosis procedure combination/per-diem payment system as of July 2018. The database represents approximately 8% of the total population in Japan and 22% of acute care hospitals as of August 2019.

Compiled patient data were anonymized by MDV after obtaining secondary usage permission from participating institutions. As the claims data were classified as anonymously processed information under the Act on the Protection of Personal Information 2003 (later amended), informed consent from individual patients and reviews or approvals from institutional review boards were not required. Ethical approval was obtained from the ethics committee of Otsuka Pharmaceutical Co., Ltd.

Study cohort

This study extracted data from patients who were diagnosed with liver cirrhosis (according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10]: K70–74) from April 2008 through September 2018. Among these, patients were included in the analysis if there was a record of hospital admission due to liver cirrhosis with at least one discharge record between January 2011 and September 2018 (study period), and identifiable Child–Pugh grades, with a score of ≥1 in all five clinical and laboratory findings of Child–Pugh classification (encephalopathy, ascites, serum total bilirubin, serum albumin, and prothrombin activity) during hospital admission. Patients aged less than 20 years at admission were excluded.

Outcome

The outcome of this study was in-hospital mortality within 1 and 3 years from the date of the earliest admission (first hospital admission due to liver cirrhosis, index date). In-hospital mortality was defined as any death due to disease or other causes that required the most medical resources recorded at discharge.

Baseline measures

Baseline characteristics included demographics (sex, age, body mass index, smoking status, and comorbidity score at hospital admission...
for liver cirrhosis). The comorbidity score was calculated based on the Charlson Comorbidity Index, but AIDS/HIV was excluded due to the lack of data. Liver cirrhosis etiology, Child–Pugh classification, its clinical and laboratory findings (i.e., encephalopathy, ascites, serum total bilirubin, serum albumin, and prothrombin activity), liver cancer, and furosemide/tolvaptan prescription were also included as baseline characteristics.

Liver cirrhosis etiology included hepatitis B virus (HBV; ICD-10 code: B16, B17.0, B18.0, or B18.1), hepatitis C virus (HCV; B17.1 or B18.2), HBV and HCV (hereafter, HBV/HCV), alcohol (K70), and none of the above (others), identified during the first hospital admission for liver cirrhosis. Liver cirrhosis etiology was identified from the disease name(s) recorded as the main disease, subdisease, disease requiring hospitalization, disease for which the most medical resources or second most medical resources were used, and disease was identified as a comorbidity at admission or during hospitalization.

The Child–Pugh classification (grade A, B, or C) during the first hospital admission for liver cirrhosis was determined according to the scoring system, using five clinical and laboratory findings of encephalopathy, ascites, serum total bilirubin, serum albumin, and prothrombin activity. Each of these findings was scored separately, with each score ranging from 1 to 3 points, and a total score was calculated to determine the Child–Pugh grade for each patient (grade A, 5–6 points; grade B, 7–9 points; grade C, ≥10 points). Ascites volume level was classified by the Child–Pugh grade as follows: none when the score was 1 point; mild when the score was 2 points; and moderate to large when the score was 3 points.

Liver cancer with liver cirrhosis was identified according to any of the following criteria: (i) liver cancer (ICD-10 code: C22) recorded as the disease requiring hospitalization, or disease identified as a complication at the first hospital admission for liver cirrhosis; (ii) at least one in-hospital liver cancer diagnosis record during a 1-year period prior to the date of hospital admission as the main disease, subdisease, disease requiring hospitalization, disease for which the most medical resources or second most medical resources were used, or disease identified as a complication; (iii) liver cancer diagnosis records during 1 year prior to the date of hospital admission in outpatient records; or (iv) treatment records for liver cancer listed in Table S1, during 1 year prior to the date of hospital admission.

Furosemide prescriptions were defined as loop diuretic prescriptions (furosemide, azosemide, trasemide, bumetanide, or piletaneide) as identified in the database (Anatomical Therapeutic Chemical [ATC] code: C03A2 for all five drug classes). Spironolactone prescriptions were defined as potassium-retaining diuretic prescriptions (spironolactone or potassium canrenoate) as identified in the database (C03A1 for two drug classes). The daily loop diuretic dose and spironolactone dose in milligrams were defined as the maximum daily dose recorded during the first hospital admission for liver cirrhosis, and was calculated for each patient as the product of the drug dose per unit and the amount prescribed. Tolvaptan prescriptions were identified based on a prescription record of vasopressin V2-receptor antagonist (C03A9).

**Statistical analysis**

Baseline characteristics were summarized descriptively, with mean and standard deviation (SD) for continuous variables and with the number and percentage for categorical variables. Baseline characteristics were summarized for overall patients and patients who were stratified by liver cirrhosis etiology (HBV, HBV/HCV, HCV, alcohol, and others), Child–Pugh classification (grade A, B, and C), or ascites volume (none, mild, and moderate to large). The frequency of patients with liver cirrhosis by age and sex was also calculated.

Time to death in days from the first hospital admission to in-hospital mortality within 3 years from the date of first admission was displayed by a Kaplan–Meier survival curve among patients stratified by liver cirrhosis etiology, Child–Pugh classification, ascites, and liver cancer presence/absence. Survival beyond 3 years and loss to follow-up were treated as censored data. The log-rank test was used to compare the difference in survival for each stratification. Cumulative survival rates at 1 and 3 years were also calculated for each of these variables.

Given our previous result using the same database, which stated that tolvaptan was prescribed at a greater frequency to liver cirrhosis inpatients with Child–Pugh grade C than those with other grades, we matched patients based on their propensity to receive tolvaptan. Propensity score matching reduces treatment-selection bias in observational studies. We extracted liver cirrhosis inpatients with ascites and matched patients with and without tolvaptan prescriptions using propensity scores (1:1 caliper matching) based on baseline characteristics (sex, age, body mass index, smoking status, comorbidity score, liver cirrhosis etiology, Child–Pugh classification, ascites volume [mild/moderate to large], presence/absence of liver cancer, prescriptions and maximum daily dose of furosemide, and maximum daily dose spironolactone). Standardized differences in these baseline characteristics were calculated to ensure a balance between pre- and post-matching. Based on the mean duration of tolvaptan prescription among the pre-matching group with tolvaptan prescription, the time to death in days from the first hospital admission to in-hospital mortality within 1 year was displayed using a Kaplan–Meier survival curve between these matched groups. Cumulative survival rates at 6 months and 1 year were also calculated for each group.

No imputation was carried out for missing data. All statistical analyses were undertaken using SAS version 9.4 (SAS Institute Inc.). The threshold p-value for the test of significance was not defined in this study.

**RESULTS**

We identified 258 866 patients who were diagnosed with liver cirrhosis between April 2008 and September 2018. After excluding inpatients who were aged less than 20 years (n = 117), and who had unidentifiable Child–Pugh grades with a score of 0 or invalid data in any of the five clinical measures of the Child–Pugh classification.
In this study, life prognosis in a Japanese clinical setting was evaluated in approximately 58,000 liver cirrhosis inpatients from 372 hospitals using a large-scale administrative database. Results showed that life prognosis differed with respect to Child–Pugh classification and ascites presence/absence, but not with respect to liver cirrhosis etiology or liver cancer presence/absence.

The 1- and 3-year cumulative survival rates among liver cirrhosis inpatients according to Child–Pugh classification were 90.2% and 75.3%, 73.5% and 53.9%, and 41.9% and 28.9% for grades A, B, and C, respectively. Prognosis was clearly worse, particularly in Child–Pugh grade C inpatients, and over 70% of inpatients died within 3 years of initial hospitalization. Overall, these prognoses tended to be somewhat similar to those in the previous systematic review, which reported that the median 1-year and 2-year cumulative survival rates were 95% and 90% in grade A, 80% and 70% in grade B, and 45% and 38% in grade C.24 Meanwhile, the 3-year cumulative survival rates in a Japanese single-center study were 93.5%, 71.0% and 30.7% for grades A, B, and C, respectively.25 This tendency was similar to another Japanese report at another facility among liver cirrhosis patients receiving treatment for esophageal varices.22 Compared to the Japanese single-center studies, this relatively worse prognosis in our large-scale study, particularly among inpatients with grade A, could partially be due to the fact that this study was limited to cirrhosis inpatients.

 ascites is the most common complication among patients with cirrhosis.34 We previously clarified that over half of cirrhosis inpatients in Japan had ascites complications and prevalence was the highest in alcoholic cirrhosis.2 We found that life prognosis was worse in inpatients with ascites, and the 1- and 3-year cumulative survival rates were 51.9% and 36.3%, respectively, for those with ascites and 83.2% and 67.0%, respectively, for those without ascites. Approximately 60% of inpatients in the ascites cohort died within 3 years of initial hospitalization. With regard to overall tendency, consistent with these previous studies, prognosis for inpatients with ascites was poor, with 1- and 5-year survival rates ranging from 45% to 82% and 22% to 57%, respectively.6,8 These reports are from studies carried out over a decade ago6,8 or from a single-center study including both outpatients and inpatients in Japan (1- and 3-year survival rates of 69% and 43%, respectively).7 Our results appeared to be poorer than previous results, but they reflect the latest real-world clinical setting of hospitalized cirrhosis patients.

In contrast to the Child–Pugh classification and ascites presence/absence, the survival curves for various liver cirrhosis etiologies were similar. The main causes of chronic liver disease are HBV or HCV infection and alcohol consumption, except for those which were classified into other, but frequencies differ in each region of the world. In Asia and Africa, the number of patients with liver cancer attributable to HBV infection is high, whereas in Japan, there are many cases of liver cancer due to HCV infection.35 In recent years, HCV infection has gradually decreased, and nonviral cirrhosis, including NASH, has increased.1,2 In Europe and North America, in
| TABLE 1 | Baseline characteristics of inpatients with liver cirrhosis |
|---------------------------------|-------------------------------------------------|
| **Etiology of cirrhosis**       | **Child–Pugh classification**                  | **Ascites volume** |
| Overall (n = 57,769)            | Overall (n = 18,995)                           | Overall (n = 33,160) |
| HBV (n = 4238)                 | Grade A (n = 10,125)                           | None (n = 17,111)   |
| HBV/HCV (n = 1210)             | Grade B (n = 5811)                             | Mild (n = 10,813)   |
| HCV (n = 14,810)               | Grade C (n = 4902)                             | Moderate to large (n = 13,796) |
| Alcohol (n = 11,693)           | None (n = 2622)                                | None (n = 17,111)   |
| Others (n = 25,818)            | Mild (n = 4086)                                | Mild (n = 10,813)   |
| Male, n (%)                    | Grade C (n = 4902)                             | Moderate to large (n = 13,796) |
| Overall (n = 57,769)           | None (n = 2622)                                | None (n = 17,111)   |
| HBV (n = 4238)                 | Mild (n = 4086)                                | Mild (n = 10,813)   |
| HBV/HCV (n = 1210)             | Moderate to large (n = 13,796)                | None (n = 17,111)   |
| HCV (n = 14,810)               | None (n = 2622)                                | Mild (n = 10,813)   |
| Alcohol (n = 11,693)           | Mild (n = 4086)                                | Moderate to large (n = 13,796) |
| Others (n = 25,818)            | Moderate to large (n = 13,796)                | None (n = 17,111)   |

### Male, n (%)

| Etiology of cirrhosis | Male, n (%) |
|-----------------------|-------------|
| Overall (n = 57,769)  | 33,994 (58.8) |
| HBV (n = 4238)        | 3604 (61.1)  |
| HBV/HCV (n = 1210)    | 3398 (60.3)  |
| HCV (n = 14,810)      | 14,088 (72.1) |
| Alcohol (n = 11,693)  | 11,259 (96.7) |
| Others (n = 25,818)   | 25,147 (88.3) |

### Age, years; mean (SD)

| Etiology of cirrhosis | Age, years; mean (SD) |
|-----------------------|------------------------|
| Overall (n = 57,769)  | 69.2 (12.4)            |
| HBV (n = 4238)        | 67.7 (11.3)            |
| HBV/HCV (n = 1210)    | 68.7 (11.3)            |
| HCV (n = 14,810)      | 68.3 (11.4)            |
| Alcohol (n = 11,693)  | 71.2 (12.5)            |
| Others (n = 25,818)   | 69.6 (12.4)            |

### BMI, mean (SD)

| Etiology of cirrhosis | BMI, mean (SD) |
|-----------------------|----------------|
| Overall (n = 57,769)  | 23.4 (4.5)     |
| HBV (n = 4238)        | 23.5 (4.3)     |
| HBV/HCV (n = 1210)    | 23.3 (4.3)     |
| HCV (n = 14,810)      | 23.2 (4.5)     |
| Alcohol (n = 11,693)  | 23.4 (4.3)     |
| Others (n = 25,818)   | 23.4 (4.3)     |

### Smoking status, n (%)

| Etiology of cirrhosis | Smoking status, n (%)
|-----------------------|------------------------|
| Overall (n = 57,769)  | No (n = 29,946 (51.8))  |
| HBV (n = 4238)        | Yes (n = 21,064 (36.5)) |
| HBV/HCV (n = 1210)    | Unknown (n = 6759 (11.7)) |
| HCV (n = 14,810)      | Comorbidity score, b mean (SD) |
| Alcohol (n = 11,693)  | 2.7 (2.1)              |
| Others (n = 25,818)   | 2.8 (2.2)              |

### Child–Pugh, n (%)

| Etiology of cirrhosis | Child–Pugh, n (%) |
|-----------------------|-------------------|
| Overall (n = 57,769)  | Grade A (n = 18,995) |
| HBV (n = 4238)        | Grade B (n = 21,407) |
| HBV/HCV (n = 1210)    | Grade C (n = 17,367) |
| HCV (n = 14,810)      | None (n = 17,111)   |
| Alcohol (n = 11,693)  | Mild (n = 10,813)   |
| Others (n = 25,818)   | Moderate to large (n = 13,796) |

### Ascites volume, n (%)

| Etiology of cirrhosis | Ascites volume, n (%) |
|-----------------------|-----------------------|
| Overall (n = 57,769)  | None (n = 33,160)     |
| HBV (n = 4238)        | Mild (n = 10,813)     |
| HBV/HCV (n = 1210)    | Moderate to large (n = 13,796) |
| HCV (n = 14,810)      | None (n = 17,111)     |
| Alcohol (n = 11,693)  | Mild (n = 10,813)     |
| Others (n = 25,818)   | Moderate to large (n = 13,796) |

### Etiology of cirrhosis, n (%)

| Etiology of cirrhosis | Overall (n = 57,769) |
|-----------------------|-----------------------|
| HBV (n = 4238)        | 4238 (7.3)            |
| HBV/HCV (n = 1210)    | 1210 (2.1)            |
| HCV (n = 14,810)      | 14,810 (25.6)         |
| Alcohol (n = 11,693)  | 11,693 (20.2)         |
| Others (n = 25,818)   | 25,818 (44.7)         |
addition to liver cancer caused by HCV infection, many cases of liver cancer also develop from alcoholic cirrhosis. In the present study, mortality among inpatients with alcoholic cirrhosis was lower than that among inpatients with viral cirrhosis. The reason for a better prognosis among inpatients with alcoholic cirrhosis, who tend to be male and have Child–Pugh grade C and ascites, could be their relatively younger age compared to other etiologies. An increasing number of alcoholic cirrhosis cases and the highest proportion of inpatients with ascites were found in alcoholic cirrhosis patients, in a previous study. In this study, a poor prognosis was found when ascites was present. These findings suggest the necessity of enhanced promotion of alcohol abstinence and/or reducing alcohol consumption to prevent liver cirrhosis or its advancement. Moreover, the proportion of inpatients categorized as “other” in the liver cirrhosis etiology was the highest in this study. The proportion of inpatients with cirrhosis due to “other” causes has been increasing yearly, which might be due to an increasing number of NASH cases, as discussed previously, and the cause in patients with an unknown cause of cirrhosis due to the increasing age of patients.

Our results indicated a better prognosis at 6 months in inpatients treated with tolvaptan, with approximately 3.5 months of tolvaptan prescription on average, than in those who were not. We matched patients using the propensity score because patients treated with tolvaptan tended to have a larger volume of ascites and a worse Child–Pugh grade compared to the control group. Generally, restriction of dietary sodium intake and conventional diuretics such as aldosterone antagonists and loop diuretics are recommended for ascites treatment. However, a lower glomerular filtration rate and increased concentrations of serum creatinine and blood urea nitrogen in treatment with furosemide have been suggested. Under such circumstances, concomitant tolvaptan treatment showed sufficient efficacy and safety for the retention of body fluids in patients with cirrhosis.

In 2013, tolvaptan was approved only in Japan for the treatment of fluid retention in hepatic cirrhosis in combination with other diuretics. Recently, it has been reported that tolvaptan is less likely to cause deterioration in renal function than furosemide, and a better long-term prognosis in responders to tolvaptan, than in nonresponders, has been reported in several Japanese studies. Additionally, although the results of studies have suggested an improvement in prognosis among patients treated with tolvaptan, to date, such evidence is still insufficient because these studies had limited sample sizes and a small number of participating institutions. This is because tolvaptan is given when other diuretics do not show effectiveness and could often be given to patients with severe symptoms. In our propensity score matching, over 4000 inpatients treated with tolvaptan were analyzed, and the results were similar to those previously reported. Cirrhosis patients with low serum sodium or impaired renal function have poor prognosis. Tolvaptan treatment increases serum sodium concentration and is less likely to exacerbate renal function, which could contribute to improved prognosis.

This study has several limitations. The results are not generalizable to overall patients with liver cirrhosis in Japan, as the MDV
FIGURE 1  Distribution of age and sex in inpatients with liver cirrhosis with respect to etiology of liver cirrhosis: (a) hepatitis B virus (HBV); (b) hepatitis C virus (HCV); (c) alcohol; and (d) others.

FIGURE 2  Kaplan–Meier survival curves in inpatients with liver cirrhosis with respect to etiology of liver cirrhosis. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; SD, standard deviation.

| Etiology (n)       | n     | Cumulative survival rates (SD) | n     | Cumulative survival rates (SD) |
|--------------------|-------|-------------------------------|-------|-------------------------------|
| HBV (4,238)        | 2,025 | 0.717 (0.008)                 | 780   | 0.556 (0.010)                 |
| HBV/HCV (1,210)    | 550   | 0.729 (0.014)                 | 187   | 0.578 (0.020)                 |
| HCV (14,810)       | 6,941 | 0.690 (0.004)                 | 2,475 | 0.484 (0.005)                 |
| Alcohol (11,693)   | 4,876 | 0.740 (0.005)                 | 1,728 | 0.588 (0.008)                 |
| Other (25,818)     | 9,994 | 0.691 (0.003)                 | 3,511 | 0.569 (0.004)                 |
database includes data collected from acute care hospitals in Japan. Additionally, as we included only inpatients, the patients in this study could be those with more severe conditions. Because the medical claims data were originally entered for reimbursement purposes, the following limitations are inevitable. First, diagnosis given only for drug prescription and undertaking tests might not be fully reliable. Second, liver cirrhosis etiologies might have been overestimated. Third, due to data unavailability, some important evaluations could be missing, such as assessments of ascites volume before and after tolvaptan prescription. Furthermore, deaths in patients who were
lost to follow-up (e.g., patients transferred to another hospital) might have been missed. Finally, prescription records were used to identify the treatments. However, drug prescription does not necessarily reflect the actual administration of drugs, even though we targeted only inpatients. With these limitations in mind, our results should be interpreted with caution.

### TABLE 2 Baseline characteristics of inpatients with liver cirrhosis in control group and group prescribed tolvaptan at before and after matching with baseline characteristics using propensity scores

|                  | Before matching |                  |                  | After matching |                  |                  |
|------------------|-----------------|-----------------|-----------------|----------------|-----------------|-----------------|
|                  | Tolvaptan group | Control group   | Standardized    | Tolvaptan group | Control group   | Standardized    |
|                  | \( n = 4775 \)  | \( n = 19,834 \) | difference       | \( n = 4104 \)  | \( n = 4104 \)  | difference       |
| Sex, \( n (%) \) |                 |                 |                 |                 |                 |                 |
| Female           | 1840 (38.53)    | 7781 (39.23)    | −1.43           | 1559 (37.99)    | 1581 (38.52)    | −1.10           |
| Male             | 2935 (61.47)    | 12,053 (60.77)  |                 | 2545 (62.01)    | 2523 (61.48)    |                 |
| Age, years; mean (SD) | 68.82 (12.26) | 69.24 (12.55)    | −3.34           | 68.56 (12.22)    | 68.47 (12.66)    | 0.76           |
| BMI, mean (SD)   | 24.20 (4.88)    | 23.13 (4.39)    | 23.03           | 24.20 (4.87)    | 24.13 (4.86)    | 1.61           |
| Smoking status, \( n (%) \) |                 |                 |                 |                 |                 |                 |
| No               | 2363 (49.49)    | 10,055 (50.70)  |                 | 2017 (49.15)    | 2057 (50.12)    |                 |
| Yes              | 1881 (39.39)    | 7285 (36.73)    | 5.33            | 1658 (40.40)    | 1613 (39.30)    | 2.19           |
| Unknown          | 531 (11.12)     | 2494 (12.57)    |                 | 429 (10.45)     | 434 (10.5)      |                 |
| Comorbidity score, mean (SD) | 2.57 (2.18) | 2.78 (2.31)    | −9.48           | 2.58 (2.18)    | 2.61 (2.27)    | −1.22          |
| Child–Pugh classification, \( n (%) \) |                 |                 |                 |                 |                 |                 |
| Grade A          | 46 (0.96)       | 685 (3.45)      | −17.77          | 36 (0.88)       | 41 (1.00)       | −0.87          |
| Grade B          | 1518 (31.79)    | 7525 (37.94)    |                 | 1329 (32.38)    | 1314 (32.02)    | 2.61           |
| Grade C          | 3211 (67.25)    | 11,624 (58.61)  |                 | 2739 (66.74)    | 2749 (66.98)    | −1.74          |
| Ascites volume, \( n (%) \) |                 |                 |                 |                 |                 |                 |
| Mild             | 1022 (21.40)    | 9791 (49.36)    | −61.45          | 866 (21.10)     | 856 (20.86)     | 0.54           |
| Moderate to large | 3753 (78.60) | 10,043 (50.64)  |                 | 3238 (78.90)    | 3248 (79.14)    |                 |
| Etiology of liver cirrhosis, \( n (%) \) |                 |                 |                 |                 |                 |                 |
| HBV              | 354 (7.41)      | 1249 (6.30)     | 4.42            | 313 (7.63)      | 317 (7.72)      | −0.39          |
| HBV/HCV          | 93 (1.95)       | 340 (1.71)      |                 | 79 (1.92)       | 75 (1.83)       |                 |
| HCV              | 1277 (26.74)    | 5131 (25.87)    |                 | 1097 (26.73)    | 1117 (27.22)    |                 |
| Alcohol          | 1231 (25.78)    | 4903 (24.72)    |                 | 1077 (26.24)    | 1066 (25.97)    |                 |
| Others           | 1820 (38.12)    | 8211 (41.40)    |                 | 1538 (37.48)    | 1529 (37.26)    |                 |
| Liver cancer, \( n (%) \) |                 |                 |                 |                 |                 |                 |
| No               | 2339 (48.98)    | 10,483 (52.85)  |                 | 1984 (48.34)    | 1973 (48.08)    |                 |
| Yes              | 2436 (51.02)    | 9351 (47.15)    | 7.75            | 2120 (51.66)    | 2131 (51.92)    | −0.54          |
| Furosemide, \( n (%) \) |                 |                 |                 |                 |                 |                 |
| No               | 269 (5.63)      | 6624 (33.40)    |                 | 245 (5.97)      | 234 (5.70)      |                 |
| Yes              | 4506 (94.37)    | 13,210 (66.60)  | 79.08           | 3859 (94.03)    | 3870 (94.30)    | −0.76          |
| Furosemide, mg; mean (SD) | 33.82 (38.35) | 17.93 (27.89)  | 47.39           | 33.35 (33.73)  | 30.41 (36.31)  | 8.77          |
| Spironolactone, mg; mean (SD) | 61.98 (78.40) | 36.54 (64.19)  | 35.51           | 61.30 (74.62) | 61.25 (77.93) | 0.07          |

Abbreviations: BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; SD, standard deviation.

*BMI was calculated as weight in kilograms divided by the square of the height in meters.

†Comorbidity score was calculated based on the Charlson Comorbidity Index but AIDS/HIV were excluded due to the unavailability of data.
FIGURE 4 Kaplan–Meier survival curves in inpatients with liver cirrhosis treated with and without tolvaptan, matched using propensity scores. Abbreviation: SD, standard deviation

In this study, we investigated the real-world hospital mortality of approximately 58,000 inpatients with liver cirrhosis using a large-scale, hospital-based administrative claims database across Japan. Our results suggest a poor prognosis for cirrhosis inpatients with a worse Child–Pugh grade and ascites. Before progressing to liver cirrhosis, early diagnosis and treatment for these patients are key to preventing poor prognosis. As this study is the first large-scale study addressing the survival of patients with cirrhosis in Japan, our results will be of benefit for understanding clinical practice.

ACKNOWLEDGMENTS
Statistical support was provided by Toru Yada at EPS Corporation (Tokyo, Japan) and Tadashi Koga at Clinical Study Support, Inc. (Nagoya, Japan). Medical writing support was provided by Rie Hagihara and Mika Kawaguchi at Clinical Study Support, Inc. Both statistical and medical writing support was funded by Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). This study and open access funding for this study were funded by Otsuka Pharmaceutical Co., Ltd. Hiroshi Yatsuhashi received a research grant from AbbVie GK. The corresponding disclosure statements of Hiroshi Yatsuhashi were granted by the ethical committee of National Hospital Organization Nagasaki Medical Center (approval no. 2020138). Hiromi Sano, Takahiro Hirano, and Yoshiyuki Shibasaki are employees of Otsuka Pharmaceutical Co., Ltd.

CONFLICT OF INTEREST
This study as well as statistical and medical writing support and open access funding for this manuscript were funded by Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). Hiroshi Yatsuhashi received a research grant from AbbVie GK. Hiromi Sano, Takahiro Hirano, and Yoshiyuki Shibasaki are employees of Otsuka Pharmaceutical Co., Ltd.

DATA AVAILABILITY STATEMENTS
The data that support the findings of this study are available for purchase from Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). Restrictions apply to the availability of these data, which were used under license for this study. For inquiries about access to the dataset used in this study, please contact MDV (website, https://www.mdv.co.jp/; e-mail, ebm_sales@mdv.co.jp).

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