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Regional Differences in the Safety of Telaprevir-Based Triple Therapy for Chronic Hepatitis C in Japan: A Retrospective Pilot Cohort Study

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Abstract

Objective: The objectives were to assess regional differences in the safety outcomes of telaprevir-based triple therapy (T/PR) in Japan and evaluate a suitable generalized linear mixed model for estimating regional differences.

Design and Methods: This study targeted individuals infected with genotype 1 chronic hepatitis C virus registered in a nationwide Japanese interferon database from December 2009 to August 2015. The rate of dropout from treatment attributable to adverse events was calculated in every prefecture where ≥ 20 cases were reported. We constructed the following four models and evaluated the best-fit model based on Akaike information criterion (AIC) and Bayesian information criterion (BIC): 1) prefecture as a fixed-effect, 2) prefecture and identified confounding factors as fixed-effects, 3) prefecture as a random-effect, and 4) prefecture as a random-effect and identified confounding factors as fixed-effects.

Results: A total of 25,989 individuals from 38 prefectures were registered during the study period; among them, 1,591 from 18 prefectures were included as the study population. The dropout rate ranged from 7.0 to 23.1% among 17 prefectures. The model considering prefecture as a random-effect and confounding factors as fixed-effects showed the best-fit for the data based on both the AIC (1,108.06) and BIC (1,113.41).

Conclusion: It is difficult to determine if regional differences exist in the safety outcomes of T/PR in Japan because of the limited number of cases. However, the model using prefecture as a random-effect and other confounding factors as fixed-effects would be suitable for estimating parameters that reflect the influence of the prefecture. Further studies using the model would help inform chronic hepatitis C treatment.

Key words: telaprevir, chronic hepatitis C, real world database, retrospective cohort study

Introduction

About 130-150 million individuals are estimated to be infected with hepatitis C virus (HCV) worldwide. Of these individuals, approximately 70,000 individuals die from cirrhosis, hepatocellular carcinoma, and other diseases each year[1]. A combination of PEGylated interferon with ribavirin (PR) is the conventional treatment for chronic hepatitis C (CHC), yielding a 40-50% sustained virologic response (SVR) rate[2]. In recent years, direct-acting antiviral agents (DAAs) have also been used to treat CHC. Telaprevir is a DAA that suppresses HCV replication by inhibiting NS3/4A viral protease; it has been used in combination with PEGylated interferon-α-2b and ribavirin (T/PR) since 2011[3,4]. Although T/PR therapy increases the SVR rate to 60-70%, the side effects are more severe than those observed for PR and include additional side effects such as dermal disorders, renal disorders, and increased uric acid[3,4]. Thus, T/PR therapy should be carefully monitored to prevent side effects or when continuing treatment. In Japan, subsidies for T/PR therapy are provided to CHC patients who receive treatment at medical institutions where

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hepatologists, as designated by the Japan Society of Hepatology, work and can cooperate with dermatologists[5]. In contrast to T/PR therapy, a combination of DAAs, meaning interferon-free therapy, presents more effective and safer treatment outcomes than regimens including PR do[6]. Although it is predicted that interferon-free therapy will overcome HCV infections and prevalence, accessibility to the therapy is limited because of drug costs[7]. Providing uniform access to CHC-related medical care is essential to suppress the prevalence of HCV; further, the number of deaths related to HCV infections would decrease[8].

However, previous retrospective cohort studies have reported regional differences in outcomes of PR therapy in Japan[9,10]. This fact may reflect differences in medical practices between regions since local health care plans are carried out by prefecture units[11]. The introduction of telaprevir changed CHC treatment regimens and likely influenced regional differences. While telaprevir has improved the SVR rate, it also requires careful monitoring. Therefore, an evaluation to determine if T/PR therapy rectifies these issues is needed. Moreover, a previous study showed that a generalized linear mixed model (GLMM) considering region as a random-effect and other confounding factors as fixed-effects was suitable for analysis of regional differences in PR therapy[12]. Although a multivariate logistic regression model is often used for estimating regional differences, the study implies that such a generalized linear model does not appropriately estimate regional differences in CHC treatment[13,14]. Generalized linear models often cannot fit data that correlate among the same subject, facility, or region[15], and model parameter estimations that do not fit the data may lead to misleading results. To solve this problem, GLMM introduces a parameter that explains correlations arising from unobserved variables. Therefore, estimating regional differences in T/PR therapy using a well-fitting model is also important for accurately evaluating the uniform accessibility of T/PR therapy.

In this cohort study, we retrospectively evaluated regional differences in the safety of T/PR therapy for CHC treatment. However, changes in the treatment of CHC have accelerated since telaprevir was introduced into clinical practice; therefore, the possibility remains that we did not obtain a sufficient number of cases. The present study is a preliminary assessment of dropout rates from the treatment attributable to adverse events between each region (prefecture). Furthermore, a suitable model was assessed for estimating parameters that reflect the influence of regional differences on safety outcomes using GLMMs.

Methods

1. Study Design

The study used a nationwide Japanese interferon database constructed by the Hepatitis Information Center of the National Center for Global Health and Medicine. To construct the database, the Hepatitis Information Center invited all 47 prefectural governments to send a treatment case report form. Once the governments agreed to cooperate, they invited individuals who had received subsidies for any interferon therapy (i.e., the single use, the combination with ribavirin, or the combination with ribavirin and a protease inhibitor) against HBV or HCV infections to report their treatment details and status. If a consent was obtained from the patient, physicians who implemented the interferon therapy fulfilled the case report form and sent it to the government. Therefore, the database consists of information from subjects with HBC, HCV, or co-infection who received the treatment regimen, including interferon, with a physician evaluation. From December 2009 to August 2015, 41 prefectural governments consented to sending case reports, and of these governments, 38 sent them to the Hepatitis Information Center. The database included the following information recorded in the case reports, which were completed by physicians: sex, date of birth, interferon treatment duration, treatment start date, treatment end date, history of interferon therapy, diagnosis, interferon regimen (type of interferon, usage of ribavirin, and usage of other drugs for hepatitis), virological response (complete response, relapse, or ineffective), treatment performance (accomplishment or dropout), adverse events causing dropout from the treatment (malaise, interstitial pneumonia, cerebral hemorrhage, anemia, anorexia, thrombocytopenia, psychoneurosis, retinopathy, and any other reason), and laboratory examination results (platelet count, alanine aminotransferase [ALT] level, aspartate aminotransferase level, HCV serotype or/and genotype, and serum HCV RNA level). The Cobas® Amplicor HCV Monitor, version 2.0 (Roche Molecular Systems, Pleasanton, CA, USA) or the Cobas® TaqMan HCV Test (Roche Molecular Systems) was used to quantify serum HCV RNA levels. The SVR was defined as an undetectable viral load 24 weeks after finishing the treatment. Although adverse events were evaluated by the physicians, suspicious drugs were not collected in the case reports. Several studies using

this database are reported elsewhere[9,10,12,16,17].

The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan (#738; October 1, 2009), and complied with the Declaration of Helsinki. Written informed consent was obtained from the individuals before enrollment.

2. Eligibility Criteria

The study period was from December 2009 to August 2015. Individuals who had CHC genotype 1 and used T/PR were included. Exclusion criteria included the following: individuals having cirrhosis, individuals younger than 16 years, individuals who dropped out for reasons other than adverse events, and cases with missing data (sex, date of birth, and others). Additionally, individuals belonging to prefectures that reported < 20 cases using T/PR were excluded from the statistical analyses to accurately represent the safety of T/PR therapy in the prefecture and construct logistic regression models. Our previous studies reported an approximate dropout rate of 10% in a similar population[16,17]. Therefore, at least one dropout for the model construction analyses was assumed, and the cutoff was set at 20 cases.

3. Statistical Analysis

Descriptive statistics were calculated to summarize continuous variables as means ± standard deviation (SD) and categorical variables as frequency and percentage (%). Age, platelet count, and ALT levels were respectively divided into two categorical groups following guidelines drawn by the Japan Society of Hepatology[18]. The viral load was categorized into high (≥5.0 log IU/mL or ≥100 KIU/mL) and low (<5.0 log IU/mL or <100 KIU/mL). Dropout from T/PR therapy attributable to adverse events was used as the safety index. The overall dropout rate and the rates in each prefecture were calculated, and the reasons for dropout were analyzed. Confounding factors were identified using stepwise multivariate logistic regression analyses with a significance level for selection and elimination set at 0.150[19]. Potential confounding factors considered in this model were as follows: categorized age (≥65 years vs <65 years), sex (male vs female), categorized platelet count (<15×104/μL vs ≥15×104/μL), categorized ALT level (≥30 IU/L vs <30 IU/L), HCV viral load (high [≥5.0 log IU/mL or ≥100 KIU/mL] vs low [<5.0 log IU/mL or <100 KIU/mL]), and treatment history (initial vs re-treatment). Adjusted odds ratios (OR) and 95% confidence intervals (CI) of selected confounding factors were calculated using the obtained model. Performance of the regression model was assessed with the Hosmer-Lemeshow test[19]. p-Values ≥0.050 were considered a goodness of fit for the data. The range in dropout rates explained whether possible regional differences existed in the safety of T/PR therapy for CHC.

Selected confounding factors were considered for GLMMs as fixed-effects. In the GLMMs,

$$\log\left\{\frac{\pi_i}{1-\pi_i}\right\}=\beta_0+\beta_i x_i+\gamma_i,\ \text{where}\ \gamma_i\sim N(0,\ \sigma_i^2)$$

where π_i is the probability of dropout from the treatment due to adverse events; β_0 is the intercept; β_i is the fixed-effect parameter; x_i is the ith row of X (the design matrix of the fixed-effects); γ_i is the random-effect parameter that follows a normal distribution with mean 0 and variance σ_i^2 [20]. The following four GLMMs were constructed to calculate β_i, γ_i, and their 95% CIs: model 1 taking prefecture as a fixed-effect, model 2 taking prefecture and selected confounding factors as fixed-effects, model 3 taking prefecture as a random-effect, and model 4 taking prefecture as a random-effect and selected confounding factors as fixed-effects. Therefore, models 1 and 2 regarded prefecture as a parameter that explained the effect by itself, whereas models 3 and 4 considered prefecture as a parameter that comprehensively included several unobserved variables such as doctor experiences, the medical delivery system, or subject accessibility to the treatment. A suitable model was assessed based on each model's goodness of fit using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC)[21,22]. Of the four models examined, the model with the lowest value was considered to indicate the relative best-fit for the data in the AIC and BIC. The ranges (minimum–maximum) of point estimates for parameters from each constructed model were also reported. The wider range in the model suggests larger regional differences in the influence of T/PR between prefectures on dropout.

All data analyses were conducted using SAS software, version 9.4 for Windows (SAS institute INC., Cary, NC, USA)

Results

1. Study Population

Figure 1 shows a flow diagram of the study. A total of 25,989 individuals with HBV or HCV infection receiving any interferon treatment were registered in the database during the study period. Of these individuals, 1,819 cases

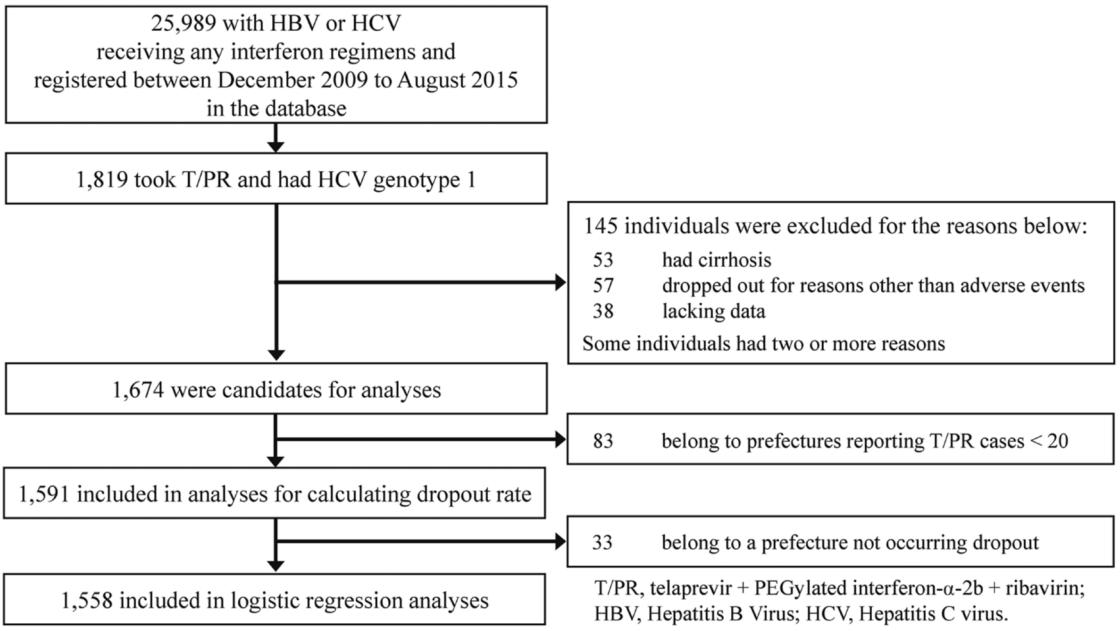


Fig. 1 Study flow diagram

were initially included; 145 were then excluded based on the following exclusion criteria: 53 had cirrhosis, 57 dropped out for reasons other than adverse events, and 38 lacked data (sex, date of birth, and others). None of these individuals were younger than 16 years. The reason for exclusion was duplicated in some individuals. Consequently, 1,674 individuals from 27 prefectures were eligible and candidates for statistical analyses. However, 83 cases were from nine prefectures that reported the number of cases using T/PR as <20; these were then excluded so that the dropout rate could be adequately calculated. Therefore, 1,591 subjects from 18 prefectures were included in the analysis set. Further, 33 cases from one prefecture were excluded from the model construction analyses because no dropouts were reported in the prefecture. Table 1 depicts characteristics of the analysis set for calculating dropout rate. Mean age was 58.10 years, and 26.5% of the population was aged ≥ 65 years. The study included 893 (56.1%) males and 693 (43.9%) females.

2. Dropout Rates

The overall dropout rate was 11.3% (180/1,591). The reasons for dropout are summarized in Table 2. In decreasing order of frequency, 27.8% (50/180) dropped out owing to malaise, 23.9% (43/180) owing to anorexia, and 16.7% (30/180) owing to anemia. Other reasons included dermal disorders, renal disorders, and increased uric acid (62.8%) (113/180). Some individuals had two or more reasons for dropping out. Dropout rates in each prefecture are shown in Fig. 2. Prefectures included in the analyses were randomly assigned numbers to maintain anonymity and were distributed throughout each region of Japan. The range of dropout rate was 7.0 to 23.1%, except for that in prefecture No.18, where dropouts did not occur. Of the 17 remaining prefectures, 5 reported at least 100 cases, and their dropout rate ranged from 7.0 to 14.1%. The other prefectures reported 20 to 85 cases, and their dropout rate ranged from 9.4 to 23.1%.

3. Multivariate Logistic Regression Analysis

In the stepwise selection procedure, categorized age (adjusted OR, 1.644; 95% CI, 1.160–2.330; $p=0.005$), sex (adjusted OR, 1.652; 95% CI, 1.199–2.277; $p=0.002$), categorized platelet count (adjusted OR, 1.629; 95% CI, 1.181–2.247; $p=0.003$), and treatment history (adjusted OR, 0.788; 95% CI, 0.570–1.088; $p=0.148$) were identified as confounding factors. The Hosmer-Lemeshow test indicated that the logistic regression model was a good fit for the data ($p=0.700$).

4. GLMMs for Analyzing Regional Differences

Figure 3 depicts β_i with 95% CI, γ_i with 95% CI, and goodness of fit for each model. The AIC and BIC for each model were as follows: model 1, AIC=1,131.81 and BIC=1,228.51; model 2, AIC=1,111.98 and BIC=1,230.16; model 3, AIC=1,125.74 and BIC=1,127.52; and model 4,

Table 1 Characteristics of study population

	T/PR
N	1,591
Age, year (mean±SD)	58.10±9.80
≥65, frequency (%)	421 (26.5)
Treatment duration, weeks (mean±SD)	23.87±10.14
Sex (male), frequency (%)	893 (56.1)
Platelet count, $\times 10^4/\mu$L (mean±SD)	16.42±5.33
<15, frequency (%)	699 (43.9)
ALT, IU/L (mean±SD)	63.11±52.53
≥30, frequency (%)	1,199 (75.4)
Treatment history, frequency (%)	
Initial	742 (46.6)
Re-treatment	844 (53.1)
Unknown	5 (0.3)
HCV viral load, frequency (%)	
High (≥5.0 log IU/mL or ≥100 KIU/mL)	1,546 (97.2)
Low (<5.0 log IU/mL or <100 KIU/mL)	45 (2.8)

Serum HCV RNA levels were quantified using the Cobas® Amplicor HCV Monitor, version 2.0 (Roche Molecular Systems, Pleasanton, CA, USA) or Cobas® TaqMan HCV Test (Roche Molecular Systems). T/PR, telaprevir + PEGylated interferon-α-2b+ribavirin; ALT, alanine amino transferase; HCV, hepatitis C virus; SD, standard deviation.

Table 2 Reasons for treatment dropouts

Reason	Frequency (%)
Malaise	50 (27.8)
Interstitial pneumonia	2 (1.1)
Cerebral hemorrhage	1 (0.6)
Anemia	30 (16.7)
Anorexia	43 (23.9)
Thrombocytopenia	5 (2.8)
Psychoneurosis	18 (10.0)
Retinopathy	10 (5.6)
Any other reason	113 (62.8)
Total dropout	180

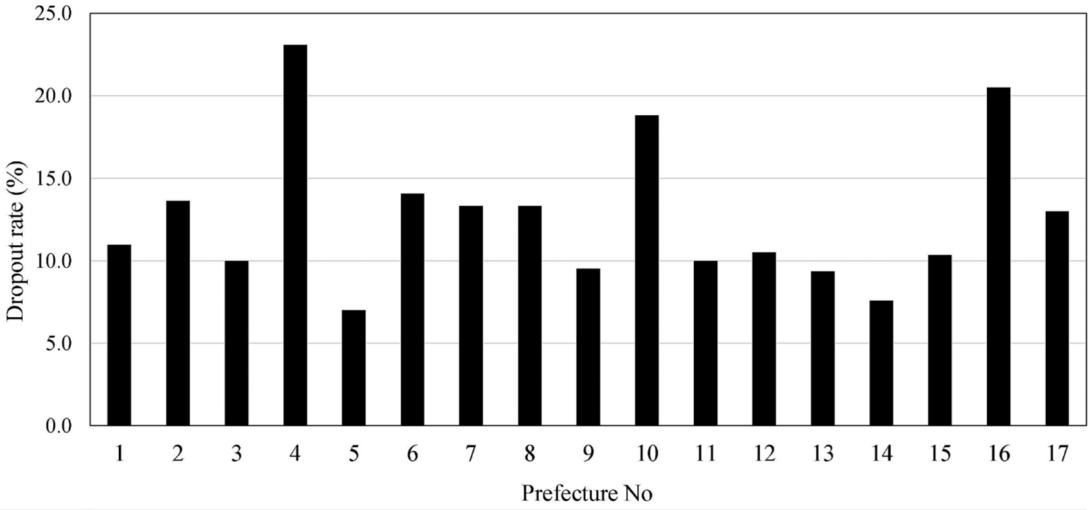
T/PR, telaprevir+PEGylated interferon-α-2b +ribavirin.

AIC=1,108.06 and BIC=1,113.41. The range of point estimates for parameters calculated was as follows: model 1, −0.890–0.490; model 2, −1.150–0.455; model 3, −0.221–0.223; model 4, −0.295–0.251.

Discussion

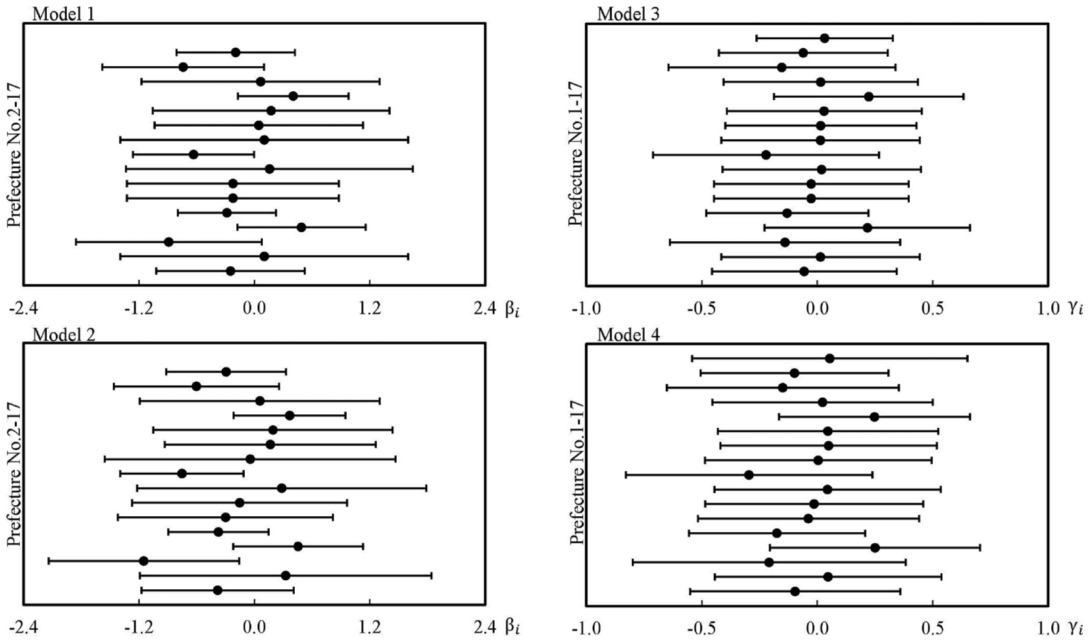
The present pilot cohort study retrospectively investigated regional differences in the safety of T/PR therapy for CHC in Japan using the nationwide interferon database. Furthermore, a suitable model for estimating parameters that reflect the influence of regional differences was assessed using GLMMs. However, it is difficult to adequately interpret the results because included cases and prefectures were limited.

The maximum dropout rate was more than three times higher than the minimum rate. This result suggests there are regional differences in dropout from the T/PR therapy, attributable to adverse events, among at least 17 prefectures. When prefectures were stratified into two groups by reported cases, the range of dropout rate in prefectures reporting <100 cases was wider than that of prefectures reporting ≥100 cases. However, the maximum dropout rate was approximately twice as high as the minimum rate among prefectures reporting ≥100 cases. Regional differences may still exist in Japan even though reported cases in each prefecture were unequal. Previous studies reported regional differences in the efficacy of PR therapy in Japan[9,10]. The authors suggest that accessibility to medical resources was a likely cause[10]. As such, if factors that were not included in the database influenced the dropout, as indicated, it may be appropriate to use prefecture as a parameter that comprehensively includes unobserved variables such as doctor experiences, the medical delivery system, or subject accessibility to treatment within the prefecture. Our data also suggest that it is preferable to include regional differences in safety analyses related to CHC treatment. It was unclear whether regional differences exist in T/PR therapy as a regimen of DAA; however, our results suggest that regional differences are present. These results



Dropout	43	9	2	6	12	28	4	4	2	16	2	4	3	18	3	8	16
Total cases	392	66	20	26	171	199	30	30	21	85	20	38	32	237	29	39	123
%	11.0	13.6	10.0	23.1	7.0	14.1	13.3	13.3	9.5	18.8	10.0	10.5	9.4	7.6	10.3	20.5	13.0

Fig. 2 Dropout rate in each prefecture



Model	Fixed-effect	Random-effect	AIC	BIC
1	Prefecture	-	1131.81	1228.51
2	Prefecture + Confounding factors	-	1111.98	1230.16
3	-	Prefecture	1125.74	1127.52
4	Confounding factors	Prefecture	1108.06	1113.41

Fig. 3 Parameters indicating the influence of prefecture on dropout rate and goodness of fit for each model

β_i is the fixed-effect parameter with 95% confidence interval; γ_i is the random-effect parameter with 95% confidence interval. The dispersion of β_i or γ_i indicates differences in the influence of telaprevir-based triple therapy between prefectures on dropout rate. AIC, Akaike information criterion; BIC, Bayesian information criterion.

provide useful information on studies related to interferon-free therapies that are mainstream of CHC treatment and to interpret results that may be influenced by regional differences.

Both AIC and BIC indicate that the model considering prefecture as a random-effect and selected confounding factors as fixed-effects results in the best fit for the data. Therefore, the GLMM was suitable for estimating parameters that reflect the influence of regional differences. The parameters calculated using the best-fitting model ranged from −0.295 to 0.251. The dispersion of the parameters could still suggest differences in the influence of T/PR between prefectures on dropout because the parameters would get centered to zero if there were no regional differences that should be considered. Additionally, the model considered categorized age, sex, categorized platelet count, and treatment history as fixed-effects. Age, sex, and platelet count are generally known as risk factors leading to side effects of T/PR therapy[23−26]. Treatment history may also affect the occurrence of side effects because physicians provide intensive medical care to successfully re-treat individuals[23]. One study examining regional differences in medication use in a heart failure trial indicated the importance of considering differences in patient characteristics for evaluating regional differences[27]. Therefore, our model estimated regional differences in T/PR therapy while considering clinically important factors. Moreover, a previous study presented similar results for the efficacy of PR therapy[12]. The present study constructed four GLMMs using a similar process and validated the use of prefectures as a random-effect and other confounding factors as fixed-effects. The possibility of applying the process and model was expanded to analyses related to telaprevir, which is a DAA.

This study has two major limitations. First, reported cases were limited. There are an estimated 1.5−2.0 million individuals infected with HCV in Japan[18]. Among them, 70% progress to CHC, and some receive government-subsidized CHC treatments. Based on statistics, the database covered ～20% of individuals who received subsidies[10]. Indeed, telaprevir had been prescribed to at least 6,900 individuals as of September 2013; however, this study only analyzed 1,591 individuals, representing approximately 1% of overall CHC individuals in Japan[24]. Thus, this study may over or under estimate the true dropout rate. Moreover, the case report flow began once individual consents were received. It is possible that individuals who had failed their treatment were reluctant to give consent. Consequently, the possibility of reporting bias may exist and have caused an underestimation of the dropout rate.

Second, the database did not include important information such as baseline creatinine levels, body weight, and drug doses, which are reportedly risk factors in the development of important drug reactions in T/PR therapy[24]. Meanwhile, data regarding these factors were not considered in the model and may differ between each prefecture. Therefore, the models constructed in this study could not be confirmed, as those factors were not considered in the stepwise selection process. The models indicate only goodness of fit for the data included in the database. In particular, drug doses were modified based on the judgment of physicians, which reflects differences in supplied medical care. Thus, there is a need to implement further studies based on more detailed information. However, considering the recent interferon-free therapy era, it is important to evaluate the clinical impacts of interferon-free therapies using a suitable model, such as the one proposed in this study.

Conclusion

Overall, although our study suggests that regional differences exist in the dropout rate from T/PR therapy for the treatment of CHC in Japan, we cannot fully confirm these results because of the limited number of cases and prefectures. The best-fitting model taking prefectures as a random-effect and selected confounding factors as fixed-effects would be suitable for estimating the parameter that explains the influence or its dispersion of the prefecture. Further studies using the proposed model should be conducted to reveal whether interferon-free therapy rectified regional differences. This would provide important findings to promote uniformity in patient access to CHC-related medical care.

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Author Contribution

RI, KI, and YK had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: RI, KI, HY, YK, NM. Acquisition of data: YK, NM. Statistical analysis and interpretation of data: RI, KI, YK. Drafting of the manuscript: RI, KI.

Conflicts of Interest: The authors declare no conflict of interest.

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