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SHORT REPORT

A descriptive analysis of acute viral hepatitis using a database with electronic medical records and claims data

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KEY WORDS

Database, electronic health records, hepatitis

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INTRODUCTION

Viral hepatitis was responsible for 1.34 million deaths worldwide in 2015 [1]. Surveillance of acute viral hepatitis is one of the priority actions identified by the World Health Organization [2]. However, accurate data on acute hepatitis are often difficult to obtain because cases are underreported.

In addition to surveillance systems, researchers have utilized administrative databases to estimate the incidence of acute hepatitis and investigate real-world management strategies. A study using the Diagnosis Procedure Combination (DPC) database in Japan estimated the national number of acute hepatitis B [3]. Another study using the DPC database reported the etiology, treatment, and mortality of patients with acute liver disease [4].

However, large-scale databases often contain limited clinical information. Most databases lack serological and clinical laboratory data, which are crucial for identifying the etiology and severity of the disease. Previous studies on acute hepatitis using the DPC database [3, 4] also had this limitation. Nevertheless, recent advances in electronic medical records allow databases to store additional information [5].

To illustrate the applicability of the databases with additional data from electronic medical records, we conducted a preliminary descriptive study of acute viral hepatitis in Japan. We used a database containing both DPC and laboratory data and investigated the etiology, treatment, and clinical course of the disease.

METHODS

Participants

The study protocol was approved by the Institutional Review Board of the Graduate School of Medicine, The University of Tokyo. We used the RWD Database, which

is maintained by the Health, Clinic, and Education Information Evaluation Institute (Kyoto, Japan) with support from Real World Data Co., Ltd. (Kyoto, Japan). The database stores data of approximately 20 million patients, collected from approximately 160 participating hospitals nationwide as of 2020 [6]. It contains DPC and health insurance claims data, as well as laboratory data extracted from the electronic medical records. Using this database, we identified patients who were hospitalized and discharged between April 2014 and March 2020 and were eligible for the DPC-based payment system. We included patients with acute viral hepatitis recorded as confirmed admission-precipitating disease (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] codes: B15, B16, or B17). We excluded patients whose claims data were unavailable and those with no laboratory test results.

Variables

We obtained the following information from the DPC data: diagnosis of acute hepatitis A, B, C, and E (ICD-10 codes B15, B16, B17.1, and B17.2, respectively) or other acute viral hepatitis (ICD-10 codes B17.1, B17.8, or B17.9), age, sex, ambulance use, Japan Coma Scale at admission, length of hospital stay, and discharge status. The following treatments during hospitalization were also identified: plasma exchange, continuous hemodiafiltration, nucleoside/nucleotide analogs (NAs) (lamivudine, adefovir, entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide), intravenous steroids, and glycyrrhizinate. The following serological test results were extracted from the database: anti-hepatitis A virus immunoglobulin M, anti-hepatitis B virus core immunoglobulin M, hepatitis B surface antigen, hepatitis C virus antibody, and anti-hepatitis E virus immunoglobulin A. A patient was categorized as positive if one or more of the tests performed during hospitalization showed positive results. Finally, the daily results of the following laboratory tests administered during hospitalization were extracted: aspartate aminotransferase, alanine aminotransferase, total bilirubin, and prothrombin time-international normalized ratio. When multiple tests of the same type were performed in one day, the maximum value was used.

Statistical Analysis

First, we compared the recorded diagnosis and serological test results for all the included patients. Further analyses were conducted in patients diagnosed with acute hepatitis A, B, C, or E, whose diagnoses matched the tests. Patients with acute hepatitis B were eligible if they were positive for either anti-hepatitis B virus core immunoglobulin M or hepatitis B surface antigen. We conducted a descriptive analysis of the patients' backgrounds, treatments, and outcomes. Descriptive statistics of laboratory data are presented as median and interquartile range of the maximum value during each patient's hospitalization. We also identified severe cases (maximum prothrombin time-international normalized ratio ≥1.5) [7] and compared NA use between severe and other hepatitis B cases. Finally, to describe the clinical course of the disease using the available laboratory data, we summarized the values for each day of hospitalization (days 1 through 14) and presented them as median and interquartile range. Statistical analyses were conducted using Stata/SE version 17.0 (College Station, TX, USA).

RESULTS

We identified 399 patients diagnosed with acute viral hepatitis. Of these, claims or laboratory data were not available for 121 patients. The recorded diagnoses and serological test results of the remaining 278 patients are presented in **Table 1**. According to the diagnosis records, there were 24, 94, 7, and 10 patients with hepatitis A, B, C, and E, respectively (N = 135 in total). The number of patients whose diagnosis records could be confirmed by the tests was 23, 70, 4, and 6 for acute hepatitis A, B, C, and E, respectively (N = 103 in total). Of the 70 patients with acute hepatitis B, 13, 24, and 33 were positive for anti-hepatitis B virus core immunoglobulin M, hepatitis B surface antigen, and both, respectively.

The characteristics of the 103 eligible patients are shown in **Table 2**. Their mean age was 47.2 years (standard deviation, 18.9 years), and the mean length of stay was 22.7 days (standard deviation, 40.4 days). Three patients (3%) underwent plasma exchange, and nine (9%) died. NAs were used in 31 of 70 patients with acute hepatitis B (44%). The following drugs were used: lamivudine (N = 4), entecavir (N = 20), tenofovir alafenamide (N = 4), entecavir and lamivudine (N = 2), and entecavir and tenofovir disoproxil fumarate (N = 1).

Table 2 also presents descriptive statistics of the laboratory data. There were 14 severe cases (13.6%), including nine patients with hepatitis B. NAs were used in seven of these nine patients (78%) with severe acute hepatitis B. Among the 61 patients with non-severe acute hepatitis B, 24 patients (39%) received NAs. Daily statistics of the laboratory data representing the clinical course are presented in **Fig. 1**.

Table 1 Results of serological tests in patients with different diagnosis records for acute viral hepatitis.

Type of test	Result	Type of acute viral hepatitis according to diagnosis record					
		A (*N* = 24)	B (*N* = 94)	C (*N* = 7)	E (*N* = 10)	Other (*N* = 143)	All (*N* = 278)
Anti-HAV IgM	Positive	23	1	0	0	2	26
	Negative	0	42	5	10	101	158
	Not tested	1	51	2	0	40	94
Anti-HBc IgM	Positive	0	46	0	0	3	49
	Negative	15	8	2	9	45	79
	Not tested	9	40	5	1	95	150
HBsAg	Positive	0	57	0	0	2	59
	Negative	20	1	4	8	105	138
	Not tested	4	36	3	2	36	81
HCVAb	Positive	0	1	4	0	1	6
	Negative	22	52	2	9	112	197
	Not tested	2	41	1	1	30	75
Anti-HEV IgA	Positive	0	0	0	6	4	10
	Negative	2	18	3	0	19	42
	Not tested	22	76	4	4	120	226

Abbreviation: anti-HAV IgM, anti-hepatitis A virus immunoglobulin M; anti-HBc IgM, anti-hepatitis B virus core immunoglobulin M; anti-HEV IgA, anti-hepatitis E virus immunoglobulin A; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.

DISCUSSION

We conducted a descriptive study of acute viral hepatitis in Japan, using a database containing DPC and laboratory data. The clinical features of 103 patients were consistent with the clinical course of acute hepatitis and similar to those reported in clinical studies. Our preliminary results illustrate the applicability of the new databases to further real-world studies.

Approximately half of the 278 patients identified in the DPC data (*N* = 135) had a diagnosis record of specific types of viruses. The results of serological tests matched the diagnoses in 103 cases (76%). However, diagnosis could not be confirmed in the remaining patients. The results of outsourced laboratory tests may not have been recorded in the hospital data. In addition, patients may have undergone testing as an outpatient or at another institution prior to referral. In this study, we excluded uncertain cases and analyzed patients with confirmed acute viral hepatitis. Patient characteristics were mostly similar to those reported in previous studies [3, 4].

We observed a high proportion of patients with acute hepatitis B who received NAs (44%) and entecavir was used most frequently. Although studies have reported the effectiveness of lamivudine for severe or fulminant hepatitis, little evidence is available for entecavir and other NAs [8–11]. Furthermore, studies have shown limited effects of NAs in improving the clinical outcomes and seroconversion rate of patients with acute hepatitis B when non-severe cases are included [12, 13]. However, NAs were used frequently in the participants of this study, possibly to prevent severe or persistent hepatitis.

The laboratory data of the patients analyzed in this database study were consistent with the clinical course of acute hepatitis and were similar to those reported in clinical studies [13, 14]. Previous database studies have relied on diagnosis and procedures to identify eligible patients and describe their conditions. However, this preliminary study illustrates the usability of databases with additional data. Multiple databases are increasingly including data from electronic medical records [5]. Thus, larger observational studies using databases with detailed clinical information may be possible in the future.

This study had several limitations. First, this was a retrospective, observational study. Because laboratory tests are performed when necessary in real-world clinical

Table 2 Characteristics and laboratory data of the 103 patients with acute viral hepatitis

Variable	
Type of hepatitis	
A	23 (23)
B	70 (68)
C	4 (4)
E	6 (6)
Sex	
Male	77 (75)
Female	26 (25)
Age, years	
0–19	2 (2)
20–39	42 (41)
40–59	29 (28)
60–79	24 (23)
≥80	6 (6)
Ambulance use	
Yes	6 (6)
No	97 (94)
Consciousness	
Clear	102 (99)
Not clear	1 (1)
Treatment	
Plasma exchange	3 (3)
Continuous hemodiafiltration	1 (1)
Intravenous steroid	13 (13)
Glycyrrhizinate	27 (26)
Outcome	
Discharged to home	91 (88)
Transferred to another hospital or facility	3 (3)
Death	9 (9)
Laboratory data[a], median [interquartile range]	
Aspartate aminotransferase, IU/L	1,227 [522, 1,975]
Alanine aminotransferase, IU/L	1,995 [931, 2,941]
Total bilirubin, mg/dL	5.8 [3.2, 11.4]
Prothrombin time-international normalized ratio	1.16 [1.05, 1.32]

Data shown as *N* (%) unless otherwise specified.
[a] Maximum value within each patient's hospitalization.

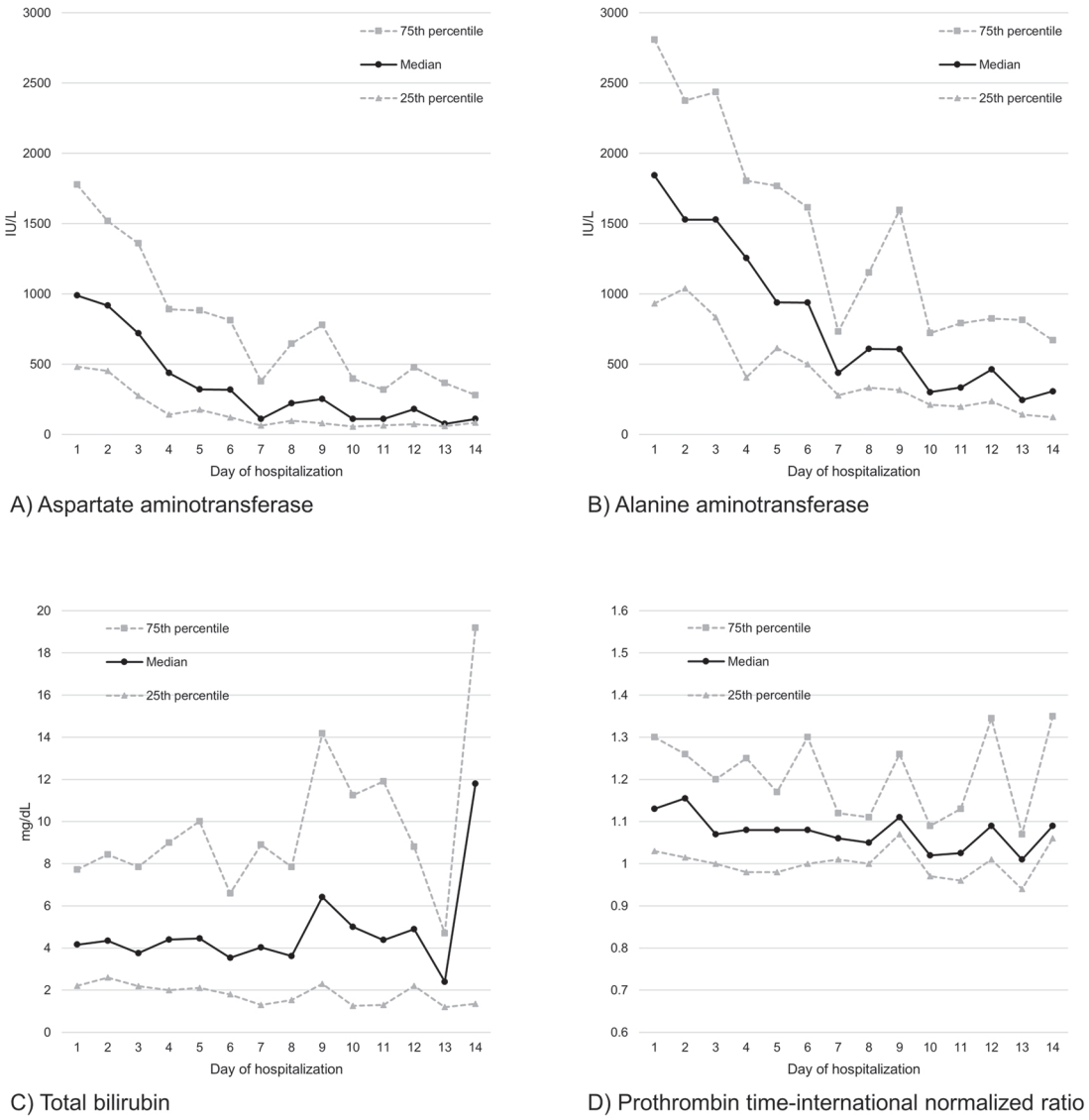

Fig. 1 **Daily statistics of laboratory data from patients with acute viral hepatitis**

practice, laboratory results may be biased toward high severity and may not necessarily reflect the natural course of patients. This bias may be especially relevant in the later days of hospitalization when the clinical courses differ across patients. Second, some cases with exacerbation of chronic hepatitis B may have been recorded as acute hepatitis. Further research with additional data on patient history may be necessary, especially for evaluating the effect of NAs. Third, we analyzed cases whose diagnosis records could be confirmed by the tests. Other cases, including those diagnosed as outpatients, were excluded. Finally, because the size of the database was relatively small, the patients and practice patterns of participating hospitals may not be representative of Japanese hospitals in general.

CONCLUSIONS

A database containing DPC and laboratory data allowed for valid and detailed descriptive analyses of patients with acute viral hepatitis. Further studies using large-scale databases with clinical data may provide evidence for the treatment of acute hepatitis.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in relation to the work presented in the manuscript.

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