The Diagnosis of Drug-induced Liver Injury: Current Diagnostic Ability and Future Challenges of the Digestive Disease Week-Japan 2004 Scale 15 Years after Its Proposal

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Abstract:
Objective This study examined whether or not the Digestive Disease Week-Japan (DDW-J) 2004 scale proposed over 15 years ago can be applied to current cases of drug-induced liver injury (DILI).

Methods The new patients group included 125 patients from 2012 to 2019 and was divided into 2 subgroups: 96 patients in the new DILI group and 29 patients in the new non-DILI group. Similarly, the old patients group included 105 patients from 1997 to 2002 and was divided into 2 subgroups: 59 patients in the old DILI group and 46 patients in the old non-DILI group. Patients were assessed by the DDW-J 2004 scale; those with a score ≥3 were defined as having DILI.

Results The total score of the new DILI group was significantly lower than that of the old DILI group [6 (1-11) vs. 6 (3-9), p=0.004]. The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) were 94.8%, 65.6%, 90.1%, and 79.2%, respectively, in the new patients group and 100%, 91.4%, 93.7%, and 100%, respectively, in the old patients group. The specificity and NPV of the new patients group were significantly lower than those of the old patients group.

Conclusion The DDW-J 2004 scale maintains a stable diagnostic ability for DILI, regardless of differences in eras and verification methods. However, differential diagnoses can affect the scoring, and new types of DILI, such as immune-related adverse events, must be addressed. Therefore, upgrading the scale should be considered.

Key words: adverse effect, diagnosis, Digestive Disease Week-Japan 2004 scale, drug-induced liver injury, Roussel Uclaf Causality Assessment Method

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Introduction

Drug-induced liver injury (DILI) due to prescription medicines, herbal medicines, over-the-counter drugs, health foods, and supplements is a liver disorder that is encountered on a daily basis. Most patients experience a good course due to the early, accurate diagnosis and discontinuation of the causative drug. However, some patients experience serious complications, such as fulminant hepatitis, requirement for liver transplant, and even death.

In Japan, the first diagnostic criteria for DILI were established in 1978 (1, 2). At that time, the principle pathogenic mechanism of DILI was thought to be an allergic reaction of the liver to drugs. Therefore, the criteria included the following immunological features: a suggestive clinical course after drug administration; symptoms related to drug allergy, such as a fever, rash, and pruritus; eosinophilia ≥6% in the peripheral blood; suggestive drug-induced lymphocyte stimulation test (DLST) results; and reappearance of liver injury following re-administration of the causal drug (1, 2). However, a national survey of DILI conducted in the latter

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half of the 1990s in Japan revealed diversity in the mechanisms, causative drugs, time to the onset of DILI, and course after the onset (1, 3). The mechanisms underlying DILI are classified as direct hepatotoxicity and idiosyncratic hepatotoxicity (4, 5). In addition, indirect hepatotoxicity related to autoimmune mechanisms has come to be considered an emerging type (4). With this increased understanding of DILI, the previous diagnostic criteria, which were biased toward allergic features, became insufficient for diagnosing current DILI cases in Japan (1, 2).

Diagnostic criteria that could be used for any type of DILI were proposed by the International Consensus Meeting (ICM) in 1990 (6) and later revised to the Roussel Uclaf Causality Assessment Method (RUCAM) scale [previously called the Council for International Organizations of Medical Sciences (CIOMS) scale] in 1993 (7). The RUCAM scale is a scoring system that considers the relationship between the drug intake and onset, clinical course after cessation of the drug, risk factors, concomitant use of drugs, differential diagnosis of alternative liver diseases, any previous information regarding the hepatotoxicity of the drug, and response to unintentional reexposure (7).

Beginning in the early 2000s, there was an opportunity in Japan to propose a diagnostic scale based on the RUCAM scale that matches the actual condition of DILI in Japan. At Digestive Disease Week-Japan 2002 (DDW-J 2002) in Yokohama, Japan, which was jointly organized with the 6th General Meeting of the Japan Society of Hepatology (JSH) held in 2002, speakers from six institutions, including the author, presented data from actual DILI cases and designed a new draft of DILI diagnostic criteria (1). After further verification (2) and revision, the DDW-J 2004 scale was proposed with consensus at DDW-J 2004 in Fukuoka, Japan, jointly organized with the 8th General Meeting of the JSH in 2004 (8). The DDW-J 2004 scale was created and validated based on actual DILI cases available at that time. Of particular note, the DDW-J 2004 scale was designed to be easy and convenient for physicians other than hepatologists to use (8, 9). Since then, the DDW-J 2004 scale has been frequently cited as a common measure for DILI in Japan in both case reports and clinical research. The English version of the digital object identifier (DOI) is currently available online at doi: 10.1111/j.1872-034X.2008.00400 (10).

However, a recent prospective study in Japan indicated that the clinical features of and pathogenic mechanism underlying DILI have changed (11, 12). In addition, many drugs with novel mechanisms of action were developed after the introduction of the DDW-J 2004 scale. Therefore, the DDW-J 2004 scale requires timely verification in order to support DILI in the current era.

The present study clarified the current clinical circumstances of DILI and evaluated whether or not the DDW-J 2004 scale, which was proposed over 15 years ago, can still be applied to current DILI cases.

### Materials and Methods

Patients were retrospectively aggregated using the medical record management systems of two different hospitals during two different eras. This study includes two patient groups. The “new patients group” consists of individuals who were enrolled between February 2012 and August 2019 at Kitasato University Medical Center (Kitamoto, Saitama, Japan), and the “old patients group” consists of individuals who were enrolled between March 5, 1997, and December 26, 2002 (i.e., before the DDW-J 2004 scale was introduced) at Kitasato University East Hospital (Sagamihara, Kanagawa, Japan).

The new patients group and old patients group were further subclassified as the new DILI group, new non-DILI group, old DILI group, and old non-DILI group, respectively, by three experts according to whether they had DILI or another liver disease based on the definitions described below; H. Yokomori and A. Shibuya were involved in the assignment of patients into the new and old patients group, respectively, and M. Watanabe validated the selection of all patients. DILI was defined as liver injury associated with drug administration. The clinical features, clinical course, and differential diagnosis of other possible causes of liver injury were evaluated comprehensively, with the final diagnosis of the experts defined as the gold standard for DILI. This approach was based on a previous report that demonstrated the superiority of expert opinions in the diagnosis of DILI (13).

Non-DILI was defined as follows: liver disease that differed from DILI, was diagnosed by experts, and occurred in patients with a history of medication use for any symptoms or underlying illness at the time liver injury was first detected. Typical non-DILI included liver diseases listed as a target for differentiation on the DDW-J 2004 scale, namely acute viral hepatitis associated with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), or cytomegalovirus (CMV); biliary tract disease; alcoholic liver disease (ALD); and shock liver. In addition, the following diseases that were suspected initially or confirmed later by experts were classified as non-DILI: chronic liver diseases, e.g. chronic viral hepatitis associated with HBV and HCV; autoimmune liver diseases, such as autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC); and metabolic disorders, such as nonalcoholic fatty liver disease (NAFLD).

Using this classification, the new patients group consisted of 96 patients with new DILI and 29 with new non-DILI, while the old patients group included 59 with old DILI and 46 with old non-DILI group (Fig. 1).

For each era, we created 2×2 contingency tables for DILI or non-DILI as defined by experts and for patients with scores ≥3 (possible or high possibility) or ≤2 (low possibility) as determined by the DDW-J 2004 scale. The sensitivity, specificity, positive predictive value (PPV), and negative pre-
dictive value (NPV) for the new and old patients groups were calculated.

**Data collection and limitations**

This study was a retrospective study. The new and old patients groups were enrolled in two different hospitals. For the new patients group, data were collected from medical records. However, medical records from most of the patients in the old patients group were not generally available. Therefore, their data were acquired from previously published papers and the contents of previous conference presentations (2, 14, 15). Furthermore, the degree of liver damage in patients in the new patients group varied from mild to severe due to advances in medical record management systems. However, the data for the old patients group were primarily collected from patients who were hospitalized.

**Statistical analyses**

Categorical patient background variables and differences in sensitivity, specificity, PPV, and NPV were analyzed by Fisher’s exact test or χ² test. Quantitative patient background variables and scores calculated by the DDW-J 2004 scale were compared. Patients in the new DILI group were more likely to have a history of alcohol use than those in the old non-DILI group. In contrast, patients in the new non-DILI group were more commonly observed than the cholestatic or mixed type in the new DILI group.

Some differences in items that might influence the DDW-J 2004 scale scoring were observed. With respect to the period from drug exposure to the onset of liver injury, no differences between the new and old DILI groups were observed. In contrast, this period was less relevant to the course of DILI in the new non-DILI group than in the old non-DILI group. Regarding the onset pattern, onset during the administration of the causative drug was more predominant in the new patients group than in the old patients group. Regarding the course after cessation of the drug, the period from drug discontinuation to the improvement of liver injury was shorter in the new DILI group than in the old DILI group. With respect to risk factors, because no pregnant women were enrolled in this study, only a history of alcohol use was subject to review. There was no marked difference in the history of alcohol use between the new and old DILI groups. In contrast, patients in the new non-DILI group were more likely to have a history of alcohol use than those in the old non-DILI group, suggesting that ALD may have been more prevalent in this group than in others. Regarding the search for non-drug causes, the exclusion diagnoses for group I diseases (HAV, HBV, HCV, ALD, gall-bladder and biliary tract disease, and shock liver) and group II diseases (EBV and CMV) specified in the DDW-J 2004 scale were compared. Patients in the new DILI group were less completely surveyed for group I and II diseases than those in the old DILI group. Previous information on drug hepatotoxicity was available for 88.7% of drugs but often unavailable for unidentified agents, such as dietary supplements. The frequency of eosinophilia did not differ markedly between the new and old DILI groups when patients without eosinophil counts were included. A DLST was per-

**Results**

Table 1 lists current and past DILI and non-DILI conditions as well as patient background characteristics. The new patients group (including both the DILI and non-DILI subgroups) was older than the old patients group. Serum levels of alanine aminotransferase (ALT) and total bilirubin were higher in the old DILI group than in the new DILI group. Regarding the DILI type, hepatocellular type was more commonly observed than the cholestatic or mixed type in the new DILI group.

Figure 1. Patients enrolled in this study. There was a 10- to 22-year gap between the 2 patient groups. New patients group: Patients with liver disease since 2012. New DILI group: Patients with drug-induced liver injury (DILI) since 2012. New non-DILI group: Patients who received medication for liver diseases other than DILI since 2012. Old patients group: Patients with liver disease before 2004. Old DILI group: Patients with DILI before 2002. Old non-DILI group: Patients who received medication for liver diseases other than DILI before 2002.
Table 1. Patient Backgrounds.

|                               | New DILI group | New non-DILI group | Old DILI group | Old non-DILI group | Differences (p value) |
|-------------------------------|----------------|--------------------|----------------|--------------------|-----------------------|
| Number of patients           | 96             | 29                 | 59             | 46                 | <0.001 <0.001         |
| Age, years                    | 65 (18-91)     | 64 (27-82)         | 51 (15-81)     | 38 (15-83)         | 1.000 0.487           |
| Male/female, n                | 46/50          | 12/17              | 29/30          | 23/23              | <0.001 <0.001         |
| ALT, IU/L                     | 204 (37-3,214) | 251 (18-4,090)     | 638 (45-5,180) | 1,139 (172-8,320)  | <0.001 <0.001         |
| ALP, IU/L                     | 507 (150-3,172)| 460 (173-8,626)    | 462 (107-2,597)| 452 (142-1,117)    | 0.854 0.543           |
| Total bilirubin, mg/dL        | 1.1 (0.3-36)   | N/A                | 1.8 (0.3-22.7) | N/A                | 0.022 N/A             |
| γGT, IU/L                     | 214 (17-1,602) | N/A                | 240 (37-1,629)| N/A                | 0.063 N/A             |
| Type of DILI, n               |                |                    |                |                    |                       |
| Hepatocellular                | 57             | 18                 | 16             | 18                 | <0.001 0.062          |
| Cholestatic or mixed          | 39             | 11                 | 43             | 28                 |                       |
| Number of cancer/non-cancer patients, n | 10/86     | 11/18              | 0/59           | 0/46               | 0.014 1              |
| Time to onset, days \(^\d\) | 24 (1-1,439)   | 83 (0-1,990)       | 15 (1-322)     | 8 (2-368)          | 0.163 0.003           |
| Drug was continued at onset, n| 74             | 18                 | 30             | 15                 | 0.001 0.017           |
| Drug was discontinued at onset, n | 22           | 11                 | 29             | 31                 |                       |
| Course after cessation of the drug, days \(^\d\) | 14 (0-120) | 14 (0-120)         | 17 (0-751)     | 15 (3-155)         | 0.035 0.040           |
| Risk factors, n              |                |                    |                |                    |                       |
| History of alcohol use        | 15             | 10                 | 4              | 5                  | 0.132 0.018           |
| No history of alcohol use     | 81             | 19                 | 55             | 41                 |                       |
| Search for non-drug causes, n |                |                    |                |                    |                       |
| Group I completion            | 46             | 15                 | 44             | 42                 |                       |
| Group II completion           | 36             | 12                 | 31             | 28                 |                       |
| Groups I and II completion   | 30             | 10                 | 29             | 26                 | 0.028 0.096           |
| Groups I and II incompletion | 66             | 19                 | 30             | 20                 |                       |
| Previous information on hepatotoxicity of the drug, n | | | | | |
| Presence                      | 88             | 25                 | 51             | 40                 | 0.415 1.000           |
| Absence                       | 8              | 4                  | 8              | 6                  |                       |
| Eosinophilia (≥6 %), n        |                |                    |                |                    |                       |
| Presence                      | 17             | 1                  | 29             | 10                 | 0.080 0.042           |
| Absence                       | 69             | 26                 | 30             | 36                 |                       |
| (unknown 10) (unknown 2)      |                |                    |                |                    |                       |
| Drug-induced lymphocyte stimulation test, n | | | | | |
| Performed                     | 23             | 1                  | 58             | 19                 | <0.001 <0.001         |
| Not performed                 | 73             | 28                 | 1              | 27                 |                       |
| Positive or semi-positive     | 11 (47.9%)     | 0 (0%)             | 24 (41.4%)     | 0 (0%)             | 0.389 <0.001          |
| Negative                      | 12 (52.1%)     | 1 (100%)           | 34 (58.6%)     | 19 (100%)          |                       |
| Response to unexpected readministration, n | | | | | |
| Presence                      | 3              | 0                  | 1              | 0                  | 1.000 1.000           |
| Absence                       | 93             | 29                 | 58             | 46                 |                       |
| Definitive diagnostic basis of DILI by experts, n | | | | | |
| Clinical course               | 80             | 27                 |                |                    |                       |
| DLST                          | 9              | 17                 |                |                    |                       |
| Liver biopsy                  | 5              | 14                 |                |                    |                       |
| Re-administration of suspicious drugs | 2            |                    |                |                    |                       |
| Liver diseases in patients without DILI, n \(^\d\) | | | | | |
| Non-alcoholic fatty liver disease | 10 (4)       |                    | 0              |                    |                       |
| Alcoholic liver disease       | 5 (2)          |                    | 0              |                    |                       |
| Biliary tract disease         | 5 (0)          |                    | 2 (0)          |                    |                       |
| Autoimmune hepatitis          | 4 (3)          |                    | 2 (0)          |                    |                       |
| Viral hepatitis               | 4 (1)          |                    | 41 (3)         |                    |                       |
| Shock liver                   | 1 (0)          |                    | 1 (1)          |                    |                       |

\(^\d\) Patients with unknown data are excluded.

\(^\d\) Numbers in parentheses indicate the number of patients with a total score of ≥3.

n: number of patients, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γGT: γ-glutamyl transpeptidase, DILI: drug-induced liver injury

Values are expressed as median (minimum - maximum), unless otherwise indicated.
formed in 98.4% of patients in the old DILI group but in only 24.0% of patients in the new DILI group. However, the positivity rate did not differ markedly between these groups. Suspected drugs were accidentally re-administered to only a few patients.

In the new DILI group, the most frequent diagnostic basis for the condition used by experts was the clinical course and a decrease in the number of liver biopsies. The reason for this decision was that the prevalence of mild DILI increased, and an invasive liver biopsy was avoided.

Regarding liver disease in new and old non-DILI patients, we noted a decrease in viral hepatitis in the new non-DILI group that was easily excluded by the DDW-J 2004 scale. All four relevant patients were diagnosed with acute hepatitis, including one associated with HBV and three associated with EBV. Viral hepatitis was more common in the old non-DILI group, including 13 cases due to HBV, 11 due to HAV, 10 due to EBV, 5 due to HCV, and 2 due to other causes. Of these 41 cases, 39 had acute hepatitis, and 2 had initially been diagnosed with chronic hepatitis C. Conversely, the incidence of NAFLD and AIH, which were difficult to exclude using the DDW-J 2004 scale, were both increased in the new non-DILI group.

Table 2 shows differences in the scores of each diagnostic item of the DDW-J 2004 scale between the new and old DILI group. Although there was no marked difference in the time to the onset (Table 1), patients in the new DILI group showed a more typical course for DILI, so a larger percentage (52.1%) received the highest score possible (2 points) than in the old DILI group (28.8%). Similarly, patients in the new DILI group also had a more typical liver injury recovery course after cessation of the drug than those in the old DILI group, so more patients (21.9%) in the new DILI group received the highest score possible (3 points) than in the old DILI group (6.8%). No marked differences in the history of alcohol use were observed. In the new DILI group, searches for non-drug causes were often not completed, so only 26.0% of patients received the highest score possible (2 points). In both subgroups, many patients were scored for items related to previous information about hepato-

### Table 2. DDW-J 2004 Scale Score Items.

| Item                                                                 | New DILI group (%) | Old DILI group (%) | p value |
|----------------------------------------------------------------------|--------------------|--------------------|---------|
| 1. Time to onset                                                     |                    |                    |         |
| 0 or 1                                                              | 46 (47.9)          | 42 (71.2)          | 0.005   |
| 2                                                                   | 50 (52.1)          | 17 (28.8)          |         |
| 2. Course after cessation of the drug                               |                    |                    |         |
| 0-2                                                                 | 75 (78.1)          | 55 (93.2)          | 0.014   |
| 3                                                                   | 21 (21.9)          | 4 (6.8)            |         |
| 3. Risk factors (ethanol)                                           |                    |                    |         |
| 0                                                                   | 81 (84.4)          | 55 (93.2)          | 0.132   |
| 1                                                                   | 15 (15.6)          | 4 (6.8)            |         |
| 4. Search for non-drug causes                                       |                    |                    | <0.001  |
| -2-1                                                                | 71 (74.0)          | 21 (35.6)          |         |
| 2                                                                   | 25 (26.0)          | 38 (64.4)          |         |
| 5. Previous information on hepatotoxicity of the drug               |                    |                    | 0.415   |
| 0                                                                   | 8 (8.3)            | 8 (13.6)           |         |
| 1                                                                   | 88 (91.7)          | 51 (86.4)          |         |
| 6. Eosinophilia†                                                    |                    |                    |         |
| 0                                                                   | 79 (82.3)          | 39 (66.1)          | 0.032   |
| 1                                                                   | 17 (17.7)          | 20 (33.9)          |         |
| 7. Drug-induced lymphocyte stimulation test                         |                    |                    | <0.001  |
| 0                                                                   | 85 (88.6)          | 35 (59.3)          |         |
| 1                                                                   | 1 (1.0)            | 7 (11.9)           |         |
| 2                                                                   | 10 (10.4)          | 17 (28.8)          |         |
| 8. Response to unexpected readministration                          |                    |                    | 1.000   |
| 0                                                                   | 93 (96.9)          | 58 (98.3)          |         |
| 3                                                                   | 3 (3.1)            | 1 (1.7)            |         |

Values are expressed as number of patients (percent). 
† The score for patients with unknown eosinophil count was set to 0.
The impact of the present study's limitations on our findings cannot be ignored. Differences in patient background characteristics and clinical findings influenced the DDW-J 2004 scale scoring. In this study, the severity of liver dam-
age at the onset was mild, and the period from discontinuation of the causative drug to the improvement of liver damage was shorter in the new DILI group than in the old DILI group. The time to the onset from the drug administration and clinical course after cessation of the drug were more consistent with DILI in the new DILI group than in the old DILI group. However, patients in the new and old patients groups were enrolled in two different hospitals, which may have influenced their backgrounds, such as the severity of liver damage, baseline diseases for which the drug was administered, and type of suspected drug. In addition, the old patients group did not include patients with cancer. While such patients were not intentionally excluded, liver dysfunction following the administration of anticancer agents might not have been registered as DILI in older medical record management systems. The factors described above are considered to be weaknesses of this retrospective study (16).

However, a review of previous peer-reviewed reports (10-12, 15) that mentioned scoring using the DDW-J 2004 scale in PubMed and the Igaku-Chuo-Zasshi database revealed that despite differences in eras, data collection method, successfully performing a differential diagnosis and DLST, and types of facilities in which the studies were conducted, the median total DDWJ-2004 scale score was 6 or 7 among patients with DILI, suggesting high sensitivity (Table 6). Concerning the type of DILI, which can also influence the time to the onset and to the improvement of DILI, the incidence of hepatocellular injury-type DILI has increased, as shown in a recent report (12).

### Changes in other liver diseases and achievement of a differential diagnosis and DLST

Changes were also observed in the list of other liver diseases that require differentiation from DILI. The DDW-J 2004 scale allows the straightforward exclusion of common viral hepatitis, such as HAV, HBV, and HCV. However, changes in the conception and epidemiology of liver disease, such as hepatitis E (HEV), for which a biological examination had not been commercialized at the time; NAFLD, which was previously not well recognized among Japanese hepatologists at the time the DDW-J 2004 scale was proposed; and acute-onset AIH (17, 18), which remains difficult

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#### Table 3. Comparison of Diagnostic Ability of DDW-J 2004 Scale in Two Different Eras.

| a) Difference in total score determined by the DDW-J 2004 scale |
|-------------------|-------------------|
| DILI group        | p value           |
| New DILI group    | 6 (1 - 11)        | 0.004 |
| Old DILI group    | 6 (3 - 9)         |       |
| Non-DILI group    |                   |
| New non-DILI group| 2 (-3 - 7)        | 0.144 |
| Old non-DILI group| 1 (-3 - 3)        |       |

Total scores are expressed as median (minimum - maximum).

| b) 2×2 contingency tables of DILI or non-DILI defined by experts, and patients with a score ≥ 3 or ≤ 2 determined by the DDW-J 2004 scale for each era. |
|---------------------------------|-----------------|
| Total score ≥ 3 or ≤ 2          |                 |
| Subgroup                        |                 |
| New DILI group, n               | 91              | 5    |
| New non-DILI group, n           | 10              | 19   |
| Old DILI group, n               | 59              | 0    |
| Old non-DILI group, n           | 4               | 42   |

n: number of patients

| c) The sensitivity, specificity, positive predictive value, and negative predictive value for the new and old patient groups. |
|---------------------------------------------------------------|
| New patients group | Old patients group | p value     |
|-------------------|-------------------|-------------|
| Sensitivity       | 94.8%             | 100%        | 0.086      |
| Specificity       | 65.6%             | 91.4%       | 0.013      |
| Positive predictive value | 90.1% | 93.7% | 0.313 |
| Negative predictive value | 79.2% | 100% | 0.005 |
to diagnose even by hepatologists, might affect the diagnostic specificity and NPV of the DDW-J 2004 scale.

In the new DILI group, most patients were tested for HBV and HCV. The exclusion of ALD by history taking and shock liver by a physical examination was also sufficient. However, examinations of biliary tract disease by imaging tests and of virus-related markers for HAV, EBV, and CMV were sometimes omitted. The number of patients who received DLST was also small.

There is no definitive biomarker for the diagnosis of DILI, so the differential diagnosis from other liver diseases and DLST is important and can affect the diagnostic ability of the DDW-J 2004 scale. However, high diagnostic costs cannot be ignored and might result in hesitation to make a detailed differential diagnosis and perform DLST.

### Diagnostic ability of the DDW-J 2004 scale for new drugs and new types of DILI

Since the proposal of the DDW-J 2004 scale, numerous drugs with novel mechanisms of action and effects, which have been adopted as major treatments for common diseases and intractable disease in various body systems, have been developed. The new patients group in the present study received some of these new drugs, and the diagnostic potential of DDW-J 2004 scale for DILI caused by these new drugs was satisfied. Nevertheless, the new DILI group included two patients who experienced tamoxifen- (one patient) and estrogen-induced steatohepatitis (one patient) (19), which were diagnosed by experts. However, the cases were each given a score of 2 points (low possibility) on the DDW-J 2004 scale. It may be difficult to diagnose drug-induced steatohepatitis using the DDW-J 2004 scale, the concept and
immune-related adverse events (irAEs) (4, 20), were not
included in this study. Other new drugs will continue to be
developed, so it is necessary to constantly verify the validity
of new drugs and add comments if any are missing to keep
the scale updated.

Table 4. Suspicious Drugs. (Continued)

| II. Old patients group | Old DILI group | Old non-DILI group |
|------------------------|---------------|-------------------|
| Anti-allergy drugs     | Number        | Name of suspicious drug | Number | Name of suspicious drug |
|                        | 3             | dexamethasone, mequitazine, phenylpropanolamine hydrochloride | 1       | mequitazine |
| Anticancer drugs       | 0             | aspirin, cold remedy×3, ibuprofen, loxoprofen sodium | 1       | tegafur/uracil |
| Anti-inflammatory       | 9             | hydrate, naproxen, OTC×2 | 19      | aspirin×3, cold remedy×2, diclofenac sodium, ibuprofen, loxoprofen sodium hydrate×4, OTC×8 |
| drugs                  | 1             | atorvastatin calcium | 0       | |
| Antilipidemic drugs    | 8             | cefcapene pivoxil hydrochloride hydrate×2, cefozopran hydrochloride, cefpodoxime proxetil, clarithromycin, fleroxacin, isoniazid, minocycline hydrochloride | 10      | azithromycin hydrate, cefaclor, cefazolin sodium hydrate, cefdinir×2, cefotiam hydrochloride, clarithromycin, erythromycin, levofloxacin×2 |
| Drugs for the          | 1             | propranolol hydrochloride | 2       | diltiazem hydrochloride, tocoferol ticotinate |
| cardiovascular system  | 4             | Hachimijigawa, Kakkontox, Mutsugan | 0       | |
| Chinese herbal         | 3             | Details are unknown. | 0       | |
| medicines              | 5             | azulene sulfate sodium and L-glutamine, cimetidine×2, ranitidine hydrochloride, teprenone | 9       | antibiotics-resistant lactic acid bacteriae, cimetidine, domperidone, famotidine×2, infliximab, OTC×3 |
| Drugs for the          | 3             | ticlopidine×3 | 0       | |
| gastrointestinal system| 2             | betamethasone, levonorgestrel | 0       | |
| Hematopoietic and      | 3             | allopurinol, camostat mesylate, tiopronin | 1       | mecobalamin |
| anticoagulant drugs    | 10            | chlorpromazine hydrochloride, halothane×2, methylphenidate hydrochloride, phenobarbital, setipiline maleate, tizanidine hydrochloride, tofisopam, tranilast, vegetanin | 0       | |
| Drugs for a urogenital  | 1             | tamsulosin hydrochloride | 2       | flavoxate hydrochloride, sildenafl citrate |
| system                 | 6             | cough medicine×2, some kind of food×2, Kallidinogenase, OTC | 1       | theophylline |

OTC: over-the-counter drug

Table 5. Differences in Total Score of Liver Injury Caused by New Drugs and Existing Drugs in the New Patients Group.

|                  | Patients who received new drugs | Patients who received existing drugs |
|------------------|--------------------------------|-------------------------------------|
|                  | ≥ 3 ≤ 2                        | ≥ 3 ≤ 2                             |
| Subgroup         | Total score                    |                                     |
| New DILI group, n| 22                            | 69                                  |
| New non-DILI group| 1                            | 9                                   |

|                  | Patients who received new drugs | Patients who received existing drugs | p value |
|------------------|--------------------------------|-------------------------------------|---------|
|                  | Sensitivity                     | Sensitivity                         | 100 %   | 93.3 % | 0.264 |
|                  | Specificity                     | Specificity                          | 83.4 %  | 60.9 % | 0.302 |
|                  | Positive predictive value       | Positive predictive value            | 95.7 %  | 88.5 % | 0.284 |
|                  | Negative predictive value       | Negative predictive value            | 100 %   | 73.7 % | 0.274 |

n: number of patients
Table 6. Review of Past Reports Showing Assessment Using the DDW-J 2004 Scale.

| Past report | Reference | 1 | 2 | 3 | 4 |
|-------------|-----------|---|---|---|---|
| **Patients and methods** | | | | | |
| Study design | Prospective Between April and December in 2005 | Retrospective Between 2002 and 2006 | Retrospective Between 1997 and 2006 | Prospective Between 2010 and 2018 |
| Setting | Single center; emergency center in an university hospital | Multicenter; 6 university hospitals and 1 general hospital | Multicenter; 19 university hospitals and 9 general hospitals | Multicenter; 22 university hospitals and 7 general hospitals |
| Inclusion criteria and gold standard of DILI | DILI that occurred during treatment at the emergency center were observed | Diagnosis was performed by experts | The diagnosis of DILI was performed according to the following: clinical course after drug administration (60%), clinical course after drug discontinuation (54%), clinical symptoms (12%), sensitivity tests (17%), diagnostic criteria (50%), liver biopsy (21%), re-administration (1.3%), and exclusion criteria (23%) | Diagnosis was performed by experts; serum levels of ALT ≥ 150 UL and/or ALP ≥ 2× upper limit of normal were required |
| Number of DILI patients | 63 | 366 | 1,676 | 307 |
| Number of non-DILI patients (control) | N/A | N/A | N/A | N/A |
| Liver diseases of patients in control groups | Gallbladder and biliary tract disease: 25, shock liver: 6, viral hepatitis: 5, alcoholic liver disease: 2, other: 4 | N/A | N/A | N/A |
| Age, years (range) | 58 (12-94) | 55 (16-92) | 55 (12-99) | 61 (17-86) |
| Male/female | 36/27 | 162/204 | 721/955 | 125/182 |
| Hepatocellular type/cholestatic or mixed type | 25 (40%)/38 (60%) | 216 (59%)/150 (41%) | 59%/41% | 64%/36% |
| Causal drugs of DILI (top three) | Details were not disclosed in the emergency center, drugs targeting the neurological system (including psychiatric agents) and antimicrobial drugs often induced DILI; anti-cancer agents and health foods were not evaluated | Anti-inflammatory (18%) Drugs targeting the neurological system (including psychiatric agents) (9%) Drugs targeting the circulatory and respiratory systems (14%) | Anti-inflammatory drugs (14.3%) Drugs targeting the neurological system (including psychiatric agents) (10.1%) Dietary supplements (10.0%) | Anti-inflammatory drugs (11%) Antimicrobial drugs (11%) Anticancer drugs (10%) |
| Time to onset from the beginning of the drug | 4 (range, 0-8) days for hepatocellular type, | ≤ 7 days: 81 (22.1%) 8-14 days: 51 (13.9%) 15-30 days 63 (17.8%) ≥ 31-60 days: 55 (15.0%) | ≤ 7 days: 411 (24.5%) 8-14 days: 228 (13.6%) 15-30 days 347 (20.7%) ≥ 31-90 days: 354 (21.1%) ≥ 91 days: 262 (15.6%) unknown: 74 (4.4%) | ≤ 7 days: 19% 8-14 days: 10% 15-30 days 24% ≥ 31-60 days: 18% ≥ 91 days: 8% |
| Time to onset from cessation of the drug | 6 (range, 2-34) days for mixed type | N/A | N/A | N/A |
| Course after cessation of the drug | 2 (range, 1-3) days for hepatocellular type, and 4 (range, 1-5) days for mixed type | 4 (range, 1-15) days for hepatocellular type, | N/A | N/A |
| Number of patients in searches for non-drug causes (group I and II) | 63 (100%) | N/A | N/A | N/A |
| Eosinophilia (≥ 6%) | 7 (11%) | N/A | 26% | 27% |
| Number of patients diagnosed as DLST/DLST positive | Not performed | DLST was performed in 198 (54%) cases, and was positive in 87 (44%) | DLST was performed in 60% of cases, and was positive in 33% | DLST was performed in 59% of cases, and was positive in 48% and semipositive in 3% |
| Response to unexpected re-administration | 3 (4.8%) | N/A | N/A | N/A |
Differences between the DDW-J 2004 scale and updated RUCAM

It should be noted that the RUCAM scale (7) and DDW-J 2004 scale (8, 11) have different purposes and uses. Nevertheless, the DDW-J 2004 scale appears to be less well-known worldwide than the RUCAM scale, considering the number of citations in reviews and research. Although the DDW-J 2004 scale was published in English (8), it remains unreadable online; this may be one of the obstacles hampering its global recognition. Note that a review article published in 2009 containing the key table of the DDW-J 2004 scale is available on the web (11).

The RUCAM scale was introduced in 1993 and updated in 2016 (21) with the purpose of assessing liver damage caused by Chinese herbs. The configuration of diagnostic items in the updated version is similar to that in the original version. Regarding alcohol intake, which is considered to be a risk factor of DILI, the amount of alcohol was determined by gender. However, the differential diagnosis was further strengthened. The seven causes of HA V , HBV , HCV , biliary tract disease, shock liver, EBV , and CMV . Subsequently, to assess allergic reactions, eosinophilia and DLST were added as diagnostic items (1).

The DDW-J 2002 causality assessment scale was evaluated to confirm its ability to accurately diagnose DILI in Japanese cases that had been overlooked using the RUCAM scale (2). Thereafter, the DDW-J 2004 scale was proposed based on the DDW-J 2002 causality assessment scale (8). In Japan, the DDW-J 2004 scale has commonly been used as a unified standard for the diagnosis of, research into, and case reporting for DILI. One of the purposes of the DDW-J 2004 scale is to function as a simple scale for use by clinicians other than hepatologists (8). It is accompanied by a detailed user manual and includes a recommendation that cases that are difficult to diagnose or have severe liver injury be promptly referred to a hepatologist (8). As mentioned above, using the DDW-J 2004 scale, inadequate differential diagnoses can reduce scores, but typical DILI patients will not be overlooked if their basic information, such as the time to the onset after administration, course after cessation of the drug, and some of them, e.g. anti-HEV-IgM, HEV-RNA, and anti-CMV-IgG, are not common in Japan.

A checklist of these diseases was included as an appended table.

The RUCAM scale aims to be a common basic tool for clinical, regulatory, publication, and expert purposes (7, 21, 22). While it is a more precise and strict causality assessment scale than the DDW-J 2004 scale (21-23), it may be inconvenient for daily clinical use for evaluation of DILI by non-hepatologists. At the DDW-J 2002 symposium that proposed a scale based on the RUCAM scale, the diagnostic item regarding “concomitant drug” in the RUCAM scale was deleted, as it carried a risk of underestimating DILI in Japanese patients, who commonly use concomitant drugs (1, 2). Indeed, 180 of 230 (78.3%) patients in this study were receiving concomitant drugs. The items for differentiation were simplified to eight common liver diseases: HA V , HBV , HCV , biliary tract disease, shock liver, EBV , and CMV. Subsequently, to assess allergic reactions, eosinophilia and DLST were added as diagnostic items (1).
risk factors, and previous information on hepatotoxicity of the drug, are met (11, 12, 15). Therefore, if the DDW-J 2004 scale is updated in the future, the updated RUCAM should be cited carefully to avoid making the diagnosis of DILI in Japan more complicated that it needs to be.

**Conclusion**

The DDW-J 2004 scale maintains a stable diagnostic ability for typical DILI, regardless of differences in patient background characteristics between eras and differences in verification methods. Nevertheless, the medical cost for the evaluation should also be considered, as well as the fact that inadequate differential diagnoses may affect scoring. While new drugs do not influence the diagnosis, new types of DILI, such as irAEs, must be addressed. Therefore, it may be time to consider updating the DDW-J 2004 scale.

The authors state that they have no Conflict of Interest (COI).

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