

Evaluation of factors associated with drug-induced liver injury using electronic medical records

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The causes and attributing factors of drug-induced liver injury (DILI) remain unclear as a result of exclusion-based diagnosis and low incidence. The aim of this study was to explore and evaluate potential drug-related causes and factors associated with DILI. Using electronic medical records (EMR) from the Seoul National University Bundang Hospital from 2003 to 2014, patients with DILI events were identified based on liver function test results. All patients with hepatic or biliary diseases were excluded. Patient characteristics, including demographics, clinical patterns, and severity of DILI were summarized and their associations were evaluated. Drugs frequently prescribed to patients exhibiting DILI within the month before their first DILI event compared to the total patient population were identified and the probabilities of hepatotoxicity associated with their use were assessed through examination of available reports. Among the 1,835 patients with laboratory test results, 1,023 were male and 1,053 were 65 years of age or older. Moderate DILI was dominant in older or male patients and cholestatic DILI tended to be more frequently identified in older patients of either sex. Cytarabine was the most frequently prescribed drug in DILI patients, followed by aprotinin and dopamine. Among the 30 most frequently prescribed drugs in DILI patients, 15 (50%) were identified as known hepatotoxic agents. In conclusion, this study evaluated differences in features of DILI among groups based on demographics and explored candidate drugs with possible associations with DILI, which has potential value reflecting real-world clinical practice.

Introduction

Drug-induced liver injury (DILI) is a major concern that can lead to liver failure or even death. Because DILI is typically diagnosed based on exclusion of other possible causes and many patients have more than one drug administered before the event, the culprit drug and attributing factors for DILI remain unclear. Indeed, one study reported that the diagnosis was incorrect or could not be proven in 25% of DILI diagnoses.[1] Furthermore, the crude annual incidence rate of DILI is low at 13.9 cases per 100,000 inhabitants in France and 19.1 cases per 100,000 in

Iceland, which may also contribute to the limited knowledge of DILI.[2,3]

There have been several attempts to determine causative drugs or characteristics of DILI. In 2011, an international DILI Expert Working Group of clinicians and scientists developed standard DILI case definitions and phenotypes in order to facilitate cross-study comparisons and collaborations.[4] Shin et al. used these standardized criteria to evaluate a large patient population based on electronic medical records (EMR).[5] By focusing on 14 medications commonly associated with hepatotoxicity, they reported results similar to those of previous prospective studies and suggested the value of large electronic healthcare databases for assessment of liver injury causality.

In this study, in contrast to a previous study,[5] we did not previously specify any drugs to be analyzed as candidate drugs

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for DILI causality. Thus, the aim of the current study was to use EMRs to explore candidate drugs that could be associated with development of DILI and to evaluate the characteristics of DILI and their associations with demographic factors.

Methods

Identification of drug-induced liver injury

DILI was defined as (i) elevated serum alanine aminotransferase (ALT) concentration to ≥ 5 times the upper limit of normal range (ULN), (ii) elevated serum alkaline phosphatase (ALP) concentration to ≥ 2 times the ULN, or (iii) elevated ALT concentration to ≥ 3 times the ULN and simultaneous elevation of total bilirubin concentration exceeding twice the ULN.[4,6] The ULNs for the laboratory tests at the Seoul National University Bundang Hospital (SNUBH) were 40 IU/L, 115 IU/L, and 1.2 mg/dL for ALT, ALP, and bilirubin, respectively.

The international DILI expert working group standards were also applied to identify not only DILI events, but also their characteristics (clinical patterns and severity).[4] Hepatocellular DILI was defined as liver chemistry thresholds of $R \geq 5$, where R is calculated as $(ALT/ALT\ ULN)/(ALP/ALP\ ULN)$. Cholestatic and mixed DILI were defined as $R \leq 2$ and $2 < R < 5$, respectively. DILI severity was classified as mild for patients who met the DILI criteria with total bilirubin concentrations < 2 times the ULN and moderate for those with total bilirubin concentrations ≥ 2 times the ULN.

Subjects

The study was approved by the institutional review board of the SNUBH (Approval number: B-1506/302-118) and the data for eligible patients were exported from the EMR database of the SNUBH, Korea. The inclusion criteria were as follows: (i) at least 1 DILI event from April 2003 to March 2014 and (ii) ≥ 19

years of age at the first DILI event. To minimize the capture of non-drug-related liver injury data, the following exclusion criteria were applied: (i) patient who had a word 'liver', 'hepato', 'hepatic', 'biliary', 'gallbladder', 'cholangi', or 'bile duct' in their diagnosis at least once; (ii) patients diagnosed with disorders of bone density and structure, other osteopathy, or fracture if they were identified as having DILI due to increased ALP values.

The analysis of drugs related to development of DILI included patients with at least one prescription one month before the first DILI event, while the evaluation of the characteristics of DILI considered patients with available ALT, ALP, or total bilirubin results two months before and after the first DILI event (Fig. 1).

Data extraction process

To explore EMR data structure in SNUBH, we randomly extracted 100 subjects who met the inclusion/exclusion criteria. The data contained laboratory and prescription data with patients' demographic characteristics such as age, sex, and diagnosis at the first DILI event. Based on these data, the statistical analysis plan and the data format to collect were determined. Laboratory data contained test date, name of the test, value and units for ALT, ALP and total bilirubin 2 months before/after the first DILI event, and prescription data included brand name, generic name, the hospital drug code, the anatomical therapeutic chemical (ATC) code of drugs prescribed 1 month before/after the first DILI event as well as age, sex, and diagnosis of patients at the first DILI event. Among the prescription data, drugs with ATC code of A11 (vitamins), A12 (mineral supplements), B05 (blood substitutes and perfusion solutions), and V (various) were excluded. Drugs not listed on the 5th level of ATC code classification system and drugs with topical use were also removed. The appropriate format and clinical range of each variable in the data set was examined by SAS 9.3 (SAS Institute Inc., Cary, NC, USA). To protect private information, the hospital's

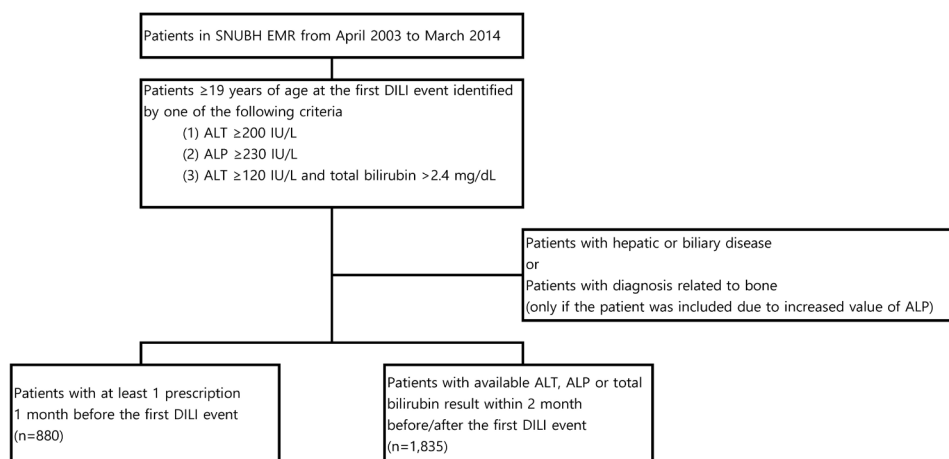


Figure 1. Inclusion and exclusion criteria and number of study patients. (SNUBH, Seoul National University Bundang Hospital; EMR, electronic medical records; DILI, drug-induced liver injury; ALT, alanine aminotransferase; ALP, alkaline phosphatase)

patient ID, which was the only data that could identify a patient, was substituted by a study specific ID at the time of data extraction.

Data analysis

Patient demographic factors (age and sex) and DILI characteristics (clinical patterns and severity) were summarized by descriptive statistics. Cochran-Mantel-Haenszel tests were used to evaluate the associations between patient demographics and DILI characteristics. All statistical analyses were performed using SAS 9.3.

To explore candidate drugs that may be associated with DILI, the frequency of drugs that had been prescribed to study patients with DILI within the month before their first DILI event were compared to those prescribed to the total patient population using the prescription ratio. The prescription ratios (n/N) were calculated as follows: the number of patients who had

been prescribed with a certain drug in the DILI population (n) over the number of patients who had been prescribed with the certain drug in the total population in EMR (N) during the same study period as the DILI population (April 2003 to March 2014). To prevent false positive results due to accidental detection, drugs prescribed to subjects resulting in only a few DILI ($n < 10$) were excluded from the analysis. For drugs with a high prescription ratio, the probability of hepatotoxicity associated with their use were assessed using the Micromedex® database.[7]

Results

Among the 1,835 patients with available ALT, ALP, or total bilirubin results two months before and after the first DILI event, 1,023 (55.8%) were male and 1,053 (57.4%) were aged 65 years or more (Table 1). The average age for study patients was 66.0 with standard deviation (SD) of 16.5 and DILI events lasted 9.3 days on average with SD of 14.1. The relationship between patient demographics (age group and sex) and DILI characteristics (clinical patterns and severity) are shown in Table 2. The clinical pattern of DILI was defined for 1,420 patients and there was a significant association between age group and clinical pattern of DILI stratified by sex ($P < 0.0001$). Cholestatic DILI tended to be more frequently identified in older patients (age ≥ 65 years) than in younger patients. The severity of DILI was also significantly associated with age group and sex. Moderate DILI was dominant in older patients after adjusting for sex ($P = 0.0104$), as well as in male patients after adjusting for age group ($P = 0.0479$) (Fig. 2).

Among the 880 patients with at least one prescription within the month before their first DILI event, cytarabine was the most frequently prescribed in DILI patients compared to all patients, with the highest prescription ratio (0.0237), followed by aprotinin and dopamine (0.0228 and 0.0144, respectively) (Table 3). Among the 30 drugs with highest prescription ratio listed in Table 3, 15 drugs were identified as causing possible hepatotoxicity in the Micromedex® database.

Discussion

This study used EMR to evaluate factors associated with liver injury

Table 1. Study patient characteristics

	Classification	Number of patients (%)
Demographics		1,835
	Male	1,023 (55.8%)
	Age ≥ 65 years	1,053 (57.4%)
Clinical pattern of drug-induced liver injury		1,420
	Cholestatic	881 (62.0%)
	Hepatocellular	344 (23.2%)
	Mixed	195 (13.7%)
Severity of drug-induced liver injury		1,835
	Mild	1,588 (86.5%)
	Moderate	247 (13.5%)

Table 2. The frequency of clinical patterns and severity of drug-induced liver injury by age group stratified by sex

	Male		Female	
	Age < 65 years	Age ≥ 65 years	Age < 65 years	Age ≥ 65 years
Clinical pattern of DILI*				
Cholestatic	169 (35.6%)	306 (64.4%)	168 (41.4%)	238 (58.6%)
Hepatocellular	94 (46.5%)	108 (53.5%)	68 (47.9%)	74 (52.1%)
Mixed	60 (56.6%)	46 (43.4%)	47 (52.8%)	42 (47.2%)
DILI severity**				
Mild	363 (41.7%)	507 (58.3%)	333 (46.4%)	385 (53.6%)
Moderate	50 (32.7%)	103 (67.3%)	36 (38.3%)	58 (61.7%)

* Significant association between age group and clinical pattern of drug-induced liver injury (DILI) after adjusting for sex ($P < 0.0001$, Cochran-Mantel-Haenszel test). ** Significant association between age group and DILI severity after adjusting for sex ($P = 0.0104$, Cochran-Mantel-Haenszel test).

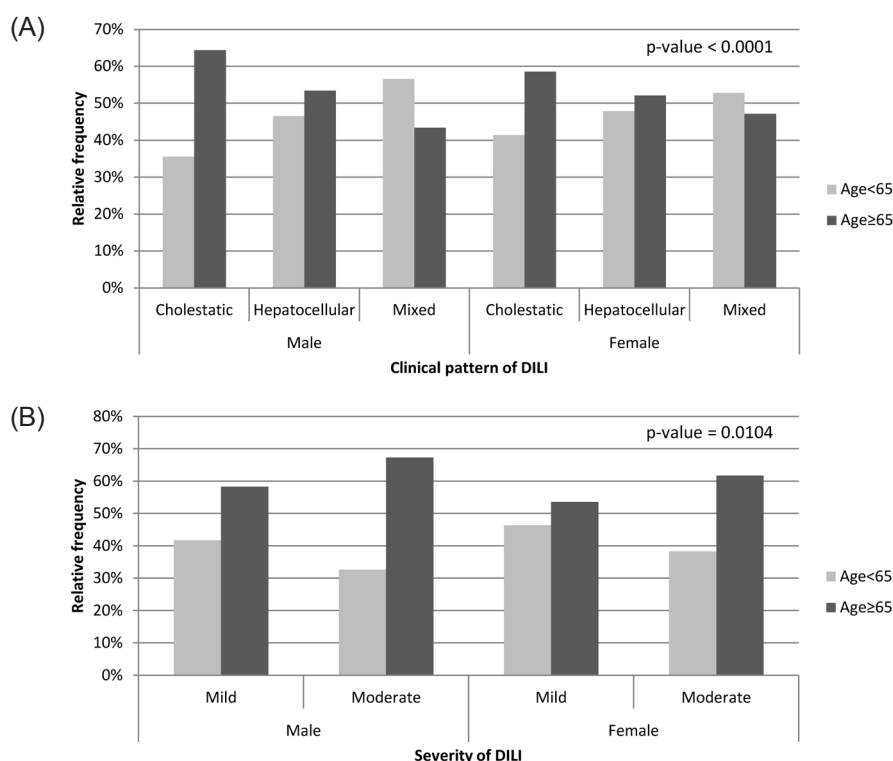


Figure 2. Frequencies of drug-induced liver injury (DILI) clinical pattern and severity by age group and sex (a, clinical pattern; b, severity; p-value from Cochran-Mantel-Haenszel test).

in patients visiting the SNUBH, focusing on demographic and liver chemistry characteristics and drugs prescribed before the liver injury event. Given DILI diagnosis is complex, the criteria for detecting case of DILI is the critical point for successful investigation. This study used standardized criteria, which will facilitate further integration of data from future investigations using the same criteria. Furthermore, this study offers a view of real-world clinical practice. The EMR data used in the study were accumulated over a 10-year period and were analyzed without any prior targeted diseases, drugs, or specific hypotheses.

Some of the results in this study are concordant with previous reports. For example, it is known that a cholestatic pattern is more frequent in an older population compared to younger adults, although the underlying mechanism for this difference remains unknown.[8,9] The severity of the DILI differed significantly according to both age group and sex in the current study. However, patients could not be classified as having severe DILI because clinical information, such as encephalopathy or ascites, necessary for classification was missing due to the unstructured nature of the data. Hence, only patients with mild or moderate DILI were identified in this study, and this limitation might have influenced the results.

Comparing the DILI patients to the total patients in EMR, cytarabine was the most frequently prescribed drug within 1

month before the DILI event. Although the exact mechanism of the hepatotoxicity is unclear, it has been reported to occur in up to 75% of leukemic patients after high dose cytarabine therapy. [10] Including cytarabine, 50% of the 30 drugs listed in Table 3 were associated with hepatotoxicity. In other words, this study identified 15 new drugs that may be associated with DILI. Although causative analysis was not performed, the prescription ratio enabled to compare the relative association of DILI with the candidate drugs. For example, isoniazid, a drug well known for its hepatotoxicity, had a prescription ratio of 0.0051, and all 30 drugs listed on Table 3 had a higher prescription ratio than isoniazid. The finding of new drugs in our study might have arisen from differences in factors associated with susceptibility to DILI among ethnicities. Suzuki et al. suggested regional divergences by reporting a unified list of drugs associated with liver injury using data sources from Spain, Sweden, and the United States.[11] They identified 369 drugs as causes of liver injury; among these, only 31 (9.7%) were identified in all three registries. Furthermore, a known ABCB11 p.444A polymorphism related to drug-induced cholestasis in European studies was not significantly associated in Japanese study findings.[12]

Based on the indications of the drugs listed on Table 3, other factors such as surgical procedures (e.g., aprotinin, suxamethonium, etomidate, and vecuronium) or hemodynamic instability (e.g., dopamine, dobutamine, norepinephrine, nitroprusside,

Table 3. Top-30 drugs frequently prescribed to patients with drug-induced liver injury compared to the total population obtained from the electronic medical record database

Drug	ATC code ^a	n ^b	N ^c	Prescription ratio (n/N)	Known hepatotoxicity ^d
Cytarabine	L01BC01	13	549	0.0237	Y
Aprotinin	B02AB01	14	614	0.0228	N
Dopamine	C01CA04	181	12591	0.0144	N
Piperacillin and enzyme inhibitor	J01CR05	81	5917	0.0137	Y
Dobutamine	C01CA07	76	5929	0.0128	N
Suxamethonium	M03AB01	33	2621	0.0126	N
Norepinephrine	C01CA03	123	9809	0.0125	N
Amiodarone	C01BD01	44	3818	0.0115	Y
Etomidate	N01AX07	72	6312	0.0114	N
Vincristine	L01CA02	11	985	0.0112	Y
Imipenem and enzyme inhibitor	J01DH51	17	1671	0.0102	Y
Piperacillin	J01CA12	21	2078	0.0101	Y
Amikacin	J01GB06	46	4774	0.0096	N
Vancomycin	J01XA01	76	8061	0.0094	N
Milrinone	C01CE02	15	1679	0.0089	Y
Phytomenadione	B02BA01	77	9157	0.0084	Y
Insulin (human)	A10AB01	138	17719	0.0078	N
Nitroprusside	C02DD01	18	2314	0.0078	N
Hydralazine	C02DB02	16	2162	0.0074	Y
Furosemide	C03CA01	292	41265	0.0071	Y
Ornithine oxoglurate	A05BA06	12	1705	0.0070	unavailable
Aztreonam	J01DF01	19	2706	0.0070	Y
Vasopressin	H01BA01	43	6380	0.0067	Y
Dolasetron	A04AA04	11	1713	0.0064	Y
Meropenem	J01DH02	17	2661	0.0064	Y
Vecuronium	M03AC03	230	38146	0.0060	N
Phenylephrine	C01CA06	98	16434	0.0060	N
Tetracosactide	H01AA02	25	4210	0.0059	N
Methotrexate	L01BA01	20	3392	0.0059	Y
Captopril	C09AA01	31	5319	0.0058	Y

a, Anatomical therapeutic chemical code; b, Number of patients who had been prescribed with the candidate drug in the drug-induced liver injury (DILI) population; c, Number of patients who had been prescribed with the certain drug in the total population in electronic medical record; d, Data based on Micromedex®.

vasopressin, and phenylephrine) might have been causative of liver injury rather than the drug itself. In addition, ornithine oxoglurate, which is a drug administered in hepatitis or liver cirrhosis patients, is also listed on Table 3, and this suggests that patients with preexisting hepatic dysfunction may not be excluded completely from the DILI population. After excluding drugs that are considered relatively unrelated to DILI, the remaining 19 agents were possible drugs associated with DILI

and most exhibited the hepatotoxicity reported in the Micromedex® database. For four of these 19 drugs (amikacin, vancomycin, insulin, and tetracosactide), there was no information about hepatotoxicity in the database, although there are several reports suggesting the possibility of liver injury of vancomycin. A wide range of hepatotoxicity, ranging from abnormalities in liver function tests to liver failure after vancomycin administration, has been reported in association with drug reaction with

eosinophilia and systemic symptoms (DRESS) syndrome.[13,14] On the other hand, amikacin has been classified as an unlikely cause of clinically apparent liver injury.[15] To date, there is no information available elucidating the hepatotoxic mechanism of insulin and tetracosactide to the best of our knowledge.

In addition to the incomplete exclusion of drugs that were not associated with DILI, all drugs prescribed by primary physicians, over the counter drugs, and herbs were not present in the data from the SNUBH, since the SNUBH is a referral hospital. Considering that herbal medications have been reported to be a principal cause of DILI and prescribed medication accounts for only 20.8% of cases in Korea, these agents might have acted as a confounding factor in this study.[16]

While large data extracted from databases such as EMRs offer many research advantages, especially for rare diseases or events, they also have inherent disadvantages. Furthermore, a retrospective study has native limitations of uncontrolled conditions and the possibility of the existence of hidden factors. This study also presented difficulties in distinguishing the effects of specific drugs or demographic factors from extrinsic factors. Incorporating data for invasive procedures, hospitalization periods, or duration of use of suspected drugs would be helpful for future studies. Non-structured data such as subjective symptoms, dietary supplements, or drug compliance should also be considered.

In conclusion, this study evaluated differences in features of DILI among groups based on demographics and explored candidate drugs having a possible association with DILI events. Although we were unable to clearly conclude the causative drugs of DILI, the approach in this study using relatively large clinical data might be helpful for future research.

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Conflict of interest

The authors declare that they have no conflict of interest.

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