Incidence, characteristic and risk factors of drug-induced liver injury in hospitalized patients: a matched case-control study

• WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT:

- Liver injury was usually associated with severe COVID-19, some drugs prescribed in COVID-19 patients are potentially hepatotoxic
- There are many drugs used clinically that have not been found to have liver toxicity.
- The risk factors for DILI are unclear.

• WHAT THIS STUDY ADDS:

- We counted the common drugs that are prone to DILI among hospitalized patients.
- Comparison of drug differences with LiverTox.
- Patients with hyperlipidemia, cardiovascular disease, pre-existing liver disease, and surgical history may increase the risk of DILI.

Abstract: Aims: The diagnosis of drug-induced liver injury (DILI) is relatively complex, involving a wide variety of drugs. The purpose of this study is to use algorithms to quickly screen DILI patients, count incidence rates and find risk factors. **Methods:** The Adverse Drug Events Active Surveillance and Assessment System-2 was used to extract the data of hospitalized patients in 2019 according to the set standards, then the RUCAM was used to evaluate patients who meet the standards. A retrospective case-control study was conducted according to suspected drugs, length of hospital stay, height and weight matched controls, and logistic regression was used to

find risk factors. **Results:** Among the 156,570 hospitalized patients, 480 patients (499 cases) of DILI were confirmed, and the incidence of DILI was 0.32%. Anti-infective agents, antineoplastic agents, non-steroidal anti-inflammatory drugs (NASIDs) were the major category of causative drugs causing DILI, and the highest incidence of DILI caused by agent of voriconazole. The latency period and hospital stay of patients with cholestasis was relatively long. Patients with hyperlipidemia (AOR: 1.884), cardiovascular disease (AOR: 1.465), pre-existing liver disease (AOR: 1.827) and surgical history (AOR: 1.312) were likely to be risk factors for DILI. **Conclusions:** The incidence of DILI in hospitalized patients was uncommon (0.32%), and its pathogenic drugs were widely distributed. LiverTox's information could assist in the diagnosis of DILI. The incidence of DILI in many drugs was seriously underestimated. It is recommended to focus on patients with hyperlipidemia, cardiovascular disease, pre-existing liver disease, and surgical history.

Keywords: drug-induced liver injury, incidence, risk factors, LiverTox, hospitalized patients

1. Introduction:

Drug induced liver injury (DILI) is a rare adverse drug reaction that can be induced by chemical drugs, traditional Chinese medicine (TCM), natural medicine (NM), biological agents, health products and dietary supplements[1]. DILI involves a wide distribution of drugs, update as of November 25, 2020, LiverTox in the United States has collected 1,093 related drug information, involving descriptions of more than 1,200 agents. Its records of extensively used for a prolonged period drugs are more accurate, recently approved or not yet widely used drugs and herbals are less accurate[2]. The drugs recorded in LiverTox are mostly used in Europe and the United States, and there are also differences with other regions. Diagnosis of DILI is very challenging. It is

necessary to rule out liver damage caused by other causes at the time of diagnosis. Then, according to the time of liver damage, improvement upon after stopping the drug, and the re-challenging test, combined with the potential hepatotoxicity and clinical characteristics of the drug for synthesis analysis[3-6]. Although liver injury is not the main cause of death in coronavirus disease 2019(COVID-19) patients, elevated ALT and AST are usually observed in hospitalized patients[7]. Liver injury was usually associated with severe COVID-19[8], some drugs prescribed in COVID-19 patients are potentially hepatotoxic[9]. Further research will be required to determine which drugs may be associated with elevated serum transaminases in COVID-19 patients. In order to facilitate the clinical discovery of drugs that may cause liver damage and compare the differences in the use of drugs between our hospital and the West, we retrospectively analyzed the patient information of the First Medical Center of the PLA General Hospital in 2019, assessed the DILI patients who met the criteria and analyzed possible risk factors.

2. Methods:

2.1 Patient admission process

The research population involved in our study was hospitalized patients from January 1, 2019 to December 31, 2019. We used Adverse Drug Events active surveillance and assessment system-II, (ADE-ASAS-II) to extract patient information from the hospital information system (HIS), and set the conditions of the system in accordance with the DILI diagnostic criteria recommended by the International Serious Adverse Event Consortium (iSAEC)[10]: Alanine aminotransferase (ALT) ≥ 5 upper limit of normal (ULN) or alkaline phosphatase (ALP) ≥ 2ULN or total bilirubin(TBL) ≥ 2ULN. If any of these conditions were met, the alarm would be triggered. The system is an adverse event warning system independently developed by our hospital, which can automatically

retrieve and alert suspected patients according to condition settings to improve work efficiency. The stability and accuracy of the system have been verified many times[11,6,12]. The researchers screened the alarmed patients, for patients with TBL≥2ULN, combined with their ALT index evaluation on the day, patients with ALT≥3ULN entered the next stage, and patients with the other two conditions entered the next stage directly.

Next, patients with abnormal liver enzymes caused by the disease were excluded based on the patient's medical history, and the remaining patients were scored using the RUCAM scale. The scoring was completed by the cooperation of pharmacists and physicians. The causality score ranges from -9 to 14 points. According to the scores, it is divided into highly probable (≥9), probable (6–8), possible (3–5), unlikely (1–2) or excluded (<0)[4]. Patients with RUCAM ≥ 6 points were directly included in the case group, and patients with 3-5 points were evaluated back-to-back again by the investigator based on the patient's medical history and disease progression. The results are consistent and identified as positive patients. The patient consults an expert for the final judgment. Patients with less than 3 points were excluded. The inclusion of DILI patients is shown in Figure 1.

2.2 Control matching method

Control matching criteria: ① Hospitalized in our hospital during the same period; ② Used the same suspected drugs; ③ Non-DILI patients with normal liver enzymes; ④ Height ±5cm; ⑤ Weight ±5Kg; ⑥Hospitalization time ±7 days. Two controls were matched for each positive patient.

2.3 LiverTox Categorization and Liver injury Type

LiverTox is a website established by the National Institute of Diabetes and Digestive and Kidney Diseases in cooperation with the National Library of Medicine and the DILI Network

Research Group, dedicated to providing physicians and pharmacists with up to date and comprehensive DILI clinical information. LiverTox is a dynamic website whose resources start with a limited amount of drug information, then gradually established, including all commercially available drugs and dietary supplements that have potential to cause liver injury[2]. LiverTox categorization the relevance of drugs and DILI based on published literature, which has been widely reported, describing cases including case series> 50 cases are defined as Category A; case reports between 12 and 50 cases are defined as Category B; fewer than 12 recognized cases are classified as Category C; a single case report seems to be related to the drug, but fewer than 3 cases reported in the literature are classified as Category D; despite extensive use, there is no evidence that the drug has caused liver injury is classified as Category E. A certain drug is suspected of causing liver injury or idiopathic acute liver injury, but there is no convincing literature report that is tentatively designated as E*, and there may not be enough information on the risk of liver injury to be classified as Category X; For drugs that do not cause DILI at normal doses, drugs with hepatotoxicity after overdose are added [HD] (high doses) after classification to distinguish[2]. We compared the drugs involved in this study with LiverTox's reports, and classified them according to the corresponding standards. The drugs not recorded in LiverTox were labeled N.

The type of liver injury was calculated based on the R value, which is (ALT value÷ALT ULN) ÷ (ALP value÷ALP ULN). The R value ≥ 5 was defined as hepatocellular injury, <2 was cholestasis injury, and the value between 2 and 5 was mixed injury[13]. We calculated the type of liver injury based on the time when the liver enzyme reached the highest value after the patient took the drug. The latency period of DILI was the time from the start of drug use to the first

detection of abnormal serum liver chemistry.

2.4 Statistical analysis

ADE-ASAS-II was used to collect and export data. Data processing was performed using Microsoft SQL Server 2016(13.0.1601.5; Microsoft Corporation, USA), and the matching of statistical content and comparison used SPSS 25.0 (version 25.0; SPSS, IBM Corporation, USA). The basic information of the patients used descriptive statistics. The mean ± standard deviation of the patients who obey the normal distribution in the continuous variables used the student t test; the median ± quartiles of the patients who do not obey the normal distribution (IQRs, Q1, Q3), using the Mann-Whitney-U test, using count and percentage as categorical variables. The variables with odds ratios (OR)<0.1 in the univariate regression were included in the multivariate regression, and adjusted odds ratios (AOR) and 95% confidence intervals (CI) were calculated.

3. Results:

3.1 Basic patient information

The HIS recorded a total of 201,299 hospitalized patients, 111,958 males and 89,341 females. Among them, there were 156,570 patients with complete liver enzyme indexes. ADE-ASAS-II alarmed 7,777 patients (8,437 cases) after scanning the data in HIS according to the standard. After the researchers used the RUCAM scale to evaluate, 480 positive patients (499 cases) were finally included, and the incidence of DILI was 0.32%. The male to female ratio of DILI patients was 1.4:1, the median age was 53 years (IQRs: 35,66), the average BMI was 22.38±4.38 Kg/m^2, and 51.70% of the patients were hospitalized for the first time. Twenty-four patients (5%) died during hospitalization. Highly probable patients 4 cases, probable 297 cases, and possible 198 cases. The median length of the patient's hospital stay was 25 days, and the patient's detailed information is shown in Table 1. The three types of liver damage had no significant differences in

age, gender, and height. The number of patients with hepatocellular injury was the largest (52.91%), and the patients with cholestasis had the longest incubation period (median 31 days). Interestingly, we found that the weight of patients with hepatocellular injury is higher than the other two types, and there is still a lack of corresponding literature support, see Table 2 for details. The distribution of the three types of hospital stay is shown in Figure 2.

3.2 Distribution of drugs and incidence of DILI

In 499 cases of DILI patients, the first suspected drugs involved 15 categories of 156 drugs, and anti-infective agents accounted for the highest proportion (44.69%), followed by antineoplastic agents and non-steroidal anti-inflammatory drugs (NSAIDs). The detailed drug categories are shown in Figure 3. Cefoperazone, Voriconazole, and Meropenem have the most frequency. In terms of morbidity, voriconazole, amikacin, fluconazole, and ifosfamide were common (≥1% and <10%), with voriconazole having the highest incidence (1.33%), and other drugs are uncommon (≥ 0.1% and <1%). Refer to the drug Categorization in LiverTox, this study contains 27 types of Category A, 24 types of Category B, 19 types of Category C, 18 types of Category D, 19 types of Category E, 5 types of Category E*, and undocumented Category N 44 kinds. There were 6 kinds of drugs related to dosage, all of which belong to Category A, see Table 3 for details.

3.3 Analysis of DILI-related risk factors

According to suspected drugs, height, weight, length of hospital stay, the positive patients were matched as controls. 474 positive patients were successfully matched with 948 non-DILI controls. The information of the two groups of patients is shown in Table 4. Univariate regression showed that age, hyperlipidemia, cardiovascular disease, tumor, pre-existing liver disease and

surgical history were significantly different between the case group and the control group. The above $p<0.1$ factors were included in the multivariate regression, and the results are shown in Table 5. Hyperlipidemia (AOR: 1.884, 95%CI: 1.097-3.239), cardiovascular disease, (AOR: 1.465, 95% CI: 1.09-1.967), pre-existing liver disease (AOR: 1.827, 95% CI: 1.344-2.483), surgical history(AOR: 1.312, 95%CI: 1.036-1.662) may be risk factors for DILI, while the AOR of age and tumor was less than 1.

4. Discussion:

The incidence of DILI in hospitalized patients was uncommon (0.32%). An article in mainland China found that the annual incidence of DILI in the general population to be 23.80 per 100,000 persons[14], and the actual result may be higher. Compared with the information of France and Iceland, 13.9-19.1 people develop DILI per 100,000 persons[15,16], while those in Spain, the United States and other countries were even lower (2.7-3.42/100,000)[17,18]. This may be related to the medication habits and genetic polymorphisms of the East and the West. Studies have found that the HLA-B*35:01 allele in Chinese patients is a risk factor for the Chinese herbal medicine (Polygonum multiflorum) to cause DILI[19]. A study on compound sulfamethoxazole causing DILI also found that there are significant differences in HLA genes among patients of different races[20], and HLA genes affect the susceptibility of patients. Inpatients use drugs more frequently, so the incidence in the hospital is much higher than that in the general population. Our results showed that the incidence rate in hospital patients was 13 times higher than that of the general population in mainland China.

The ratio of male to female in hospitalized patients was 1.3:1, and the ratio of male to female among 499 patients was 1.4:1, with no significant difference (P=0.879), the more male patients in

our research may be related to the number of hospital visits. 10.42% of DILI were minors (52 cases, <18 years old), 78.85% of minors were admitted to the hospital for tumors (42.31% were acute lymphoblastic leukemia, 25.00% were osteosarcoma), antineoplastic agents were the main cause of DILI in minors. In terms of hospital stay, the median of patients in our hospital was about 7 days, the median of DILI was 25 days, and the hospital stay of DILI patients was significantly longer. It is not clear whether DILI leads to a longer hospital stay, or whether the longer hospital stay leads to an increased risk of DILI exposure. Therefore, in the risk factor analysis, we balanced hospital stay as a control variable to reduce its interference with the results. The median latency period of DILI was 6 days (IQRs: 3, 12). A study published by BJöRNSSON *et al* in Gastroenterology in 2013 found that the median latency period of inpatients was 9 days (IQRs: 6-14)[16], our incubation period data was relatively short, which may be related to the time of hospital inspections. Compared with inpatients, the latency period of outpatients was significantly longer. Iceland had found that the median latency period of outpatients was 30 days (IQRs: 9–97) [16]. Research in Mainland China has shown that the incubation period of all types of liver injury exceeds 30 days (Including outpatients)[14]. Outpatient prescriptions were mostly oral drugs. The latency period of these drugs was generally long. Secondly, it is also related to the detection time of liver enzymes of patients. Outpatients cannot monitor liver enzymes in time when they are out of hospital.

Cephalosporins were the most common drugs classification that cause DILI[21]. In general, the cephalosporins have been associated with little hepatotoxicity and only rare instances of DILI due to these agents have been published, ceftriaxone is the most reported cephalosporin in Europe and America[2]. Indeed, other cephalosporins have a lower incidence of liver injury in addition to

ceftriaxone, and our research results also confirm this. The only difference was cefoperazone, the highest-ranked agents. Cefoperazone was less used in the West, but it was used in a larger amount in China and was the drug that causes the largest number of liver damage. The difference in drug applications has led to deviations. Voriconazole was a known cause of clinically acute drug-induced liver injury[22]. It was the agent with the highest incidence (1.33%), testing for TBL and aminotransferase levels was recommended at the time of starting and weekly during the first month of voriconazole therapy and monthly thereafter[2]. Carbapenem rarely cause obvious and long-lasting liver damage, mostly cholestasis, which may be related to immune mechanisms, and liver damage caused by meropenem is usually mild and self-limited[23]. The statistical results showed that the median latency period of meropenem, biapenem and imipenem was 7 days, mainly cholestasis (24 cases, 63.16%), and the prognosis was mostly good (92.11% recovered).

Levofloxacin in LiverTox was updated on March 10, 2020, after the update, it was adjusted from Category B to Category A. The latency period was usually short (average latency period of 10 days), and most patients had sudden onset, accompanied by hepatocellular injury (60%) or cholestatic injury (27%) and jaundice (2 cases, 13%). Studies have found that up to 5% of patients treated with fluconazole have transient mild to moderate elevations in ALT levels, but these abnormalities were usually asymptomatic and relieved even if they continue to take the medication[24]. According to the relevant medical records of fluconazole patients, most of their liver injury occurred within one to two weeks of treatment (median 6 days). It was often accompanied by signs of hypersensitivity, such as fever (11 cases, 78.57%) and eosinophilia (4 cases, 28.57%), cholestasis and hepatocellular injury were similar (7 vs 5), and 4 patients died after medication.

Methylprednisolone is a corticosteroid drug. Because of its potent anti-inflammatory and immunosuppressive activities, it is often used as the treatment of choice for severe hepatitis[25]. However, liver injury often occurs when t given long term and in higher than physiologic doses (4 mg)[2]. The results showed that the dosage of methylprednisolone in DILI patients ranged from 16mg to 500mg, and 64% of patients with methylprednisolone had a daily dose of >100mg. Glucocorticoids have many mechanisms that cause DILI. After use, they can result in hepatic enlargement and steatosis or glycogenosis. Long-term use can also aggravate viral hepatitis; withdrawal or pulse therapy after hormone therapy can also cause hepatitis B Reactivate and worsening or de novo induction of autoimmune hepatitis[2]. The mechanism of liver damage caused by statins may also be related to autoimmune. The mild ALT elevations caused by them were usually self-limited and did not require dose modification[26,27]. The liver injury of statins was mainly hepatocellular injury (11 cases, 57.89%, ALT average value 314u L^{-1}). If the ALT level rises to 10-fold ULN, or if it continues to rise more than 5-fold or is associated with symptoms, it should be stopped.

A prospective Spanish article on DILI found that hyperlipidemia (OR: 4.26, 95% CI: 1.02–17.74, p = 0.04) may be an independent risk factor for chronic DILI (duration> 1 year), statins were the most frequent of drugs in chronic DILI episodes[28]. The results of this study showed that hyperlipidemia not only increases the risk of chronic patients, but patients with hyperlipidemia have a high risk of acute DILI after admission (OR: 1.88, 95% CI: 1.10–3.24, p = 0.02), the mechanism may be related to malnutrition leading to slow drug clearance and delay drug elimination[29]. The use of statins may also induce autoimmune hepatitis, which makes DILI more likely to occur[30]. A retrospective study in China also believes that hyperlipidemia was

related to the occurrence and severity of DILI[31]. Cardiovascular disease patients may delay the onset of DILI after taking certain drugs[32], multivariate regression showed that cardiovascular disease (AOR: 1.465, 95%CI: 1.09-1.967) is an independent risk factor for DILI. It is preliminary guessed that its mechanism may be similar to hyperlipidemia. The drugs used in the disease may induce autoimmune hepatitis, thereby increasing the risk of DILI.

A group study involving antiretroviral therapy showed that the presence of liver disease before starting treatment, including chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and alcoholic liver disease are risk factors for DILI[33,34], where the risk of DILI in HCV-3 patients is twice that of other genotypes[33,35]. COVID-19 is still a problem that humans need to overcome together. It has been reported that liver injury after COVID-19 infection is common, mainly hepatocellular injury, and the increase in aspartate aminotransferase higher than ALT, combined use of hepatotoxic drugs will increase the risk of DILI[8]. Pre-existing liver disease is one of the most common risk factors for DILI, some studies indicated that chronic liver disease may be a risk factor for severe COVID-19[36], and decompensated liver cirrhosis may be a risk factor for poor prognosis of COVID-19[37]. It is recommended that first-line medical staff pay attention to the liver enzymes of patients with pre-existing liver disease and intervene in time to prevent the progression of DILI.

In this paper, we compared the drug distribution of LiverTox and discussed the incidence and risk factors of DILI among 156,570 hospitalized populations. However, this study has some limitations: 1. The research was a single-center retrospective study, and the results may be biased; 2. The average hospital stay of cancer patients was no more than one week. DILI could not be recorded after discharge, and many Category A antineoplastic agents have not appeared in our

results. In the follow-up study, we plan to conduct a cohort study to follow up DILI patients; 3. Although there was a certain degree of balance in the selection of controls, it was still impossible to rule out the interference of the disease and the combined medication.

Conclusions:

The diagnosis of DILI requires consideration of multiple factors. The rational application of systematic screening and manual identification can improve the efficiency of group entry. DILI patients have a long hospital stay, low morbidity, and high mortality. Voriconazole was the drug with the highest incidence. The DILI characteristics of different drugs were very different. Combined with LiverTox data could facilitate clinical diagnosis. Patients with hyperlipidemia, cardiovascular disease, pre-existing liver disease, and surgical history were at higher risk of DILI and needed to be monitored.

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