Clinical Features, Risk Factors, and Prognostic Markers of Drug-Induced Liver Injury in Patients with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Abstract
Background: The liver and skin are the most common organs involved in Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Drug reactions rarely affect both organs concurrently. The clinical features, risk factors, and prognostic markers of drug-induced liver injury (DILI) in patients with SJS/TEN are not well studied. Materials and Methods: The clinical features, risk factors, and prognostic markers of DILI in patients with SJS/TEN hospitalized at the dermatology department of our hospital from January 2009 to December 2018 were retrospectively analyzed. Results: A total of 298 patients with SJS/TEN were enrolled in this study. Of them, 40 had liver injury and the rest served as control. Causative drugs mainly included antipodagrics (xanthine oxidase inhibitors occupying 100% among antipodagrics), anticonvulsants (dibenzazepine occupying 76.92% among anticonvulsants), and traditional Chinese medicines. There was a statistically significant difference between the patients with liver injury and the control group in the history of liver disease, diabetes, and hyperlipidemia (P < 0.05). Nine of the 40 patients with liver injury died. High serum total bilirubin and creatinine levels were significantly associated with poor prognosis of DILI in patients with SJS/TEN (P < 0.05). Conclusion: DILI usually occurs in patients with SJS/TEN. Pre-existing liver disease, diabetes, and hyperlipidemia are independent risk factors for DILI in patients with SJS/TEN. High serum total bilirubin and creatinine levels may be useful prognostic markers for DILI in patients with SJS/TEN.

Key Words: Drug-induced liver injury, prognostic markers, risk factors, Stevens-Johnson syndrome, toxic epidermal necrolysis

Introduction
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening severe cutaneous adverse reactions. The symptoms of these conditions rapidly transform and advance to produce extensive skin lesions, injuries to multiple organs with frequent fatal outcome.¹ Liver injury is one of the most common complications of SJS/TEN. This is mainly characterized by the abnormality of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase, and other liver parameters.² However, there has been no comprehensive analysis of the clinical features, risk factors, and prognostic markers of drug-induced liver injury (DILI) in patients with SJS/TEN. Therefore, we retrospectively analyzed the clinical features and explored the risk factors and prognostic markers of DILI among patients with SJS/TEN admitted between January 2009 and December 2018 in our department.

Materials and Methods
In this study, 298 patients with SJS/TEN hospitalized between January 2009 and December 2018 in our department of dermatology were included. Among them, 40 patients with liver injury were assigned to the case group and the remaining 258 patients served as the control group. All patients were diagnosed by two chief physicians based on guidelines reported in previous authoritative publications.³ Patients were classified as having SJS, TEN, or SJS-TEN on the basis of total liver injury in patients with Stevens–Johnson syndrome/toxic epidermal necrolysis. Indian J Dermatol 2020;65:274-8.

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DILI was defined as ≥5x upper limit of normal (ULN) for alanine aminotransferase (AST) or aspartate aminotransferase (ALT) or ≥2 ULN for alkaline phosphatase (ALP) or bilirubin ≥2 ULN with ≥3 ULN for ALT. Exclusion criteria included recent hepatitis virus infection and acute liver injury caused by other factors. DILI was grouped into three categories. An R score of 2 or less was sorted as cholestatic, between 2 and 5 as mixed and greater than 5 as hepatocellular. R = (ALT/ULN)/(ALP/ULN). Causative drugs were evaluated by Roussel Uclaf Causality Assessment Method (RUCAM). In addition, we performed Algorithm for Drug Causality for Epidermal Necrolysis (ALDEN) for SJS/TEN to further analyze the causative drugs. Similar to the RUCAM, ALDEN scores were leveraged to categorize the probability of the disease into very probable, probable, possible, unlikely, and very unlikely.

All suspicious drugs were stopped immediately at admission. The initial dose of glucocorticoids was equivalent to methylprednisolone (40–100 mg/d) intravenous drip in the early stage, and gradually decreased to oral corticosteroids until drug withdrawal. Six patients were given an intravenous immunoglobulin (IVIG) dose of 400 mg/kg/day for five days. At the same time, we provided symptomatic supportive treatment for symptoms including anti-infection, liver protection, and electrolyte supplementation.

All information about the patients such as the gender, age, causative drugs, history of allergy, history of alcohol intake, pre-existing liver disease, diabetes, hypertension, hyperlipidemia, laboratory tests, and outcomes were recorded for analysis.

**Statistical analysis**

All statistical analyses were carried out by using IBM PASS Statistic (25.0; SPSS, New York, USA). The clinical features of liver injury were descriptively analyzed in patients with SJS/TEN. Normality of data distribution was checked by the Kolmogorov–Smirnov test. The categorical data was checked by the Kolmogorov–Smirnov test. Either t test or rank sum test was used based on the results of the Kolmogorov–Smirnov test. The categorical data were tested by chi-square test or Fisher’s exact test. Multivariate logistic regression analysis was performed to identify risk factors and prognostic markers of DILI in patients with SJS/TEN. P < 0.05 was considered statistically significant.

**Results**

**Clinical features of DILI in patients with SJS/TEN**

This study included 298 patients with SJS/TEN (172 male, 126 female; with an average age of 47.99 ± 19.79 years). Among them, 40 (13.42%) had liver injury (25 male, 15 female; with an average age of 49.35 ± 21.21 years). In this study, the main clinical manifestations of DILI in patients with SJS/TEN were skin and sclera yellow staining [11 (27.50%)], fatigue [10 (25.00%)], inappetence [11 (27.50%)], and yellow coloration of urine [11 (27.50%)]. Liver discomfort was observed in six subjects (15.00%), skin itching in 24 (60.00%), fever in 35 (87.50%), and mucosal rash in 23 (57.50%). In terms of the patterns of liver injury, 14 (35.00%) patients had a hepatocellular pattern, 14 (35.00%) had a cholestatic pattern, and 12 (30.00%) had a mixed pattern of injury. With respect to severity, 23 (57.5%) patients had mild, 5 (12.5%) had moderate, and 12 (30%) had severe DILI.

According to the RUCAM score, 20 of the 40 DILI in patients with SJS/TEN were listed as probable and the rest 20 as highly probable. The ALDEN score for patients with SJS/TEN was performed. The results showed that 21 patients were categorized as very probable and 19 as probable. The top three allergic drugs were antipodagrics (xanthine oxidase inhibitors occupying 100% among antipodagrics), anticonvulsants (dibenzazepine occupying 76.92% among anticonvulsants), and traditional Chinese medicines (TCM) [Table 1].

**Risk factors for DILI in patients with SJS/TEN**

Comparison of age, gender, history of allergy, drinking history, pre-existing liver disease, and chronic underlying diseases were performed between the two groups. The results showed that there was no significant difference in age, gender, allergic history, drinking history, and hypertension. There were significant differences between the two groups in terms of pre-existing liver disease, history of diabetes, and hyperlipidemia. Univariate analysis followed by multivariate logistic regression was performed to identify the risk factors of DILI in patients with SJS/TEN. The results showed that pre-existing liver diseases, hyperlipidemia, and diabetes were independent risk factors for DILI in patients with SJS/TEN [Table 2].

**Prognostic markers for DILI in patients with SJS/TEN**

In this study, 9 patients of DILI with SJS/TEN died. To determine the prognostic markers of DILI in patients with SJS/TEN, we divided them into two groups either as the survivors or nonsurvivors. The results showed that high serum total bilirubin and creatinine levels were significantly associated with poor prognosis of DILI in patients with SJS/TEN [Tables 3 and 4].

**Discussion**

Current research suggests that the pathogenesis of drug-induced liver injury is mainly immune-mediated and metabolic-mediated mechanisms. SJS/TEN are also considered to be immune-mediated adverse drug reactions. Therefore, some studies have suggested that
DILI is associated with SJS/TEN. Previous studies have shown that the incidence rates of liver injury in patients with SJS/TEN reach 9.62%. Devarbahi et al. found the incidence of DILI in patients of SJS/TEN was 4.81% and the mortality rate of SJS/TEN reached as high as 36.11%. In this study, the incidence rates of DILI in patients with SJS/TEN was 13.42%, and the mortality rate reached 22.5%, suggesting a high incidence of liver injury and poor outcome in patients with SJS/TEN.

In this study, causality assessment for DILI in patients with SJS/TEN was evaluated by RUCAM and ALDEN scores. The results showed that the main causative drugs were antipodagrics, anticonvulsants, and traditional Chinese medicines (TCM). All antipodagrics were allopurinol, and the proportion of dibenzazepine among anticonvulsants was 76.92%. The TCM accounted for 17.5% of all causative drugs in this study. This might be caused by excessive doses, prolonged use, and complex and unclear ingredients. In addition, many TCM have been found to be potentially hepatotoxic and may activate different mechanisms of liver injury (immune allergic reactions, the biological activity of cytochrome P450 and oxidative stress), resulting in the development of DILI in patients with SJS/TEN.

Further analyses were performed to compare the gender, age, history of allergy, drinking history, pre-existing liver disease, and the chronic underlying diseases between the two groups. The results showed that the pre-existing liver disease, diabetes, and hyperlipidemia were risk factors for DILI in patients with SJS/TEN, suggesting that SJS/TEN patients with pre-existing liver disease, diabetes, and hyperlipidemia were more susceptible to liver injury. Studies have shown that patients with a history of liver disease have higher risk of drug-induced liver injury. In this study, we found that patients with SJS/TEN who had a pre-existing liver disease had significantly increased risks of developing liver injury and were more prone to severe liver damage. We argue that pre-existing liver disease, diabetes, and hyperlipidemia are risk factors for DILI in patients with SJS/TEN.

### Table 1: Causative drugs of DILI in patients with SJS/TEN (n=40)

| Class | Category | Drug* | No. of patient |
|-------|----------|-------|----------------|
| Antimicrobials (n=3) | Cephalosporins (n=2) | Ceftriaxone | 1 |
| | | Ceftazidime | 1 |
| | Penicillin (n=1) | Penicillin | 1 |
| Antipodagrics (n=11) | Xanthine oxidase inhibitors (n=11) | Allopurinol | 11 |
| Anticonvulsants (n=13) | Dibenzazepine (n=10) | Carbamazepine | 8 |
| | | Oxcarbazepine | 2 |
| | | Lamotrigine | 1 |
| | | Phenytoin | 1 |
| | | Phenobarbital | 1 |
| NSAIDs (n=4) | Anilines (n=1) | Paracetamol | 1 |
| | Pyrazolones (n=2) | Phenylbutazone | 2 |
| | Salicylates (n=1) | Aspirin | 1 |
| Others (n=12) | - | TCM | 7 |
| | | Leflunomide | 2 |
| | | Tegafur, Gimeracil and Oteracil potassium capsules | 1 |
| | | Omeprazole | 1 |
| | | Compound Danshen Tablets | 1 |

*Three patients were on two drugs each: Carbamazepine + phenobarbital, carbamazepine + lamotrigine, and aspirin + ceftriaxone.

DILI: Drug-induced liver injury; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis; TCM: Traditional Chinese medicines.

### Table 2: Comparison of risk factors of DILI in patients with SJS/TEN

| Variable | SJS/TEN with DILI (n=40) | SJS/TEN without DILI (n=258) | P |
|----------|--------------------------|-----------------------------|---|
| Age (years) | 49.35±21.21 | 47.78±19.59 | 0.932 |
| Male/female | 25/15 | 147/111 | 0.607 |
| History of allergy | 5 | 30 | 1.000 |
| Drinking history | 6 | 21 | 0.230 |
| Pre-existing liver disease† | 6 | 13 | 0.029 |
| Diabetes | 9 | 21 | 0.010 |
| Hypertension | 12 | 51 | 0.148 |
| Hyperlipidemia | 14 | 42 | 0.008 |

†Pre-existing liver disease included history of chronic viral hepatitis, alcoholic liver disease, fatty liver disease, cirrhosis, and autoimmune hepatitis in this study. P values in bold are statistically significant.
liver disease may decrease the ability of the liver to break down, transform, and clear drugs, which prolong the time of the drug in the body, and increase the incidence of DILI. In addition, pre-existing liver disease may increase the susceptibility of patients to drug-induced liver injury, which is more likely to cause liver injury.\[19\]

Relatively poor physical function of diabetic patients, together with the relatively low drug metabolism, and the accumulation of hepatotoxic substances in blood vessels are likely to cause liver injury. In addition, patients with type 2 diabetes often have abnormal lipid metabolism and changes in lipid factors, oxygen stress, and lipid peroxidation, abnormal accumulation of hepatic glycogen, and liver iron overload, which will easily result in enormous burden on the liver or liver impairment.\[18,20\]

Patients with hyperlipidemia are prone to develop liver injury due to the high level of blood lipids in the body, which may affect the metabolic level and metabolic rate of the drug in the body.

For better understanding of the markers affecting the prognosis of DILI in patients with SJS/TEN, we analyzed the clinical data of all the patients with SJS/TEN for DILI. Nine of the 40 patients with liver injury died. We argue that these patients had serious conditions and often were accompanied by multiple organ damage, and thus their prognosis was extremely poor. In this study, multivariate analysis showed that high serum total bilirubin and creatinine levels were significantly associated with poor prognosis of DILI in patients with SJS/TEN. After hepatocyte injury, the metabolism of bilirubin is impaired, leading to the release of bilirubin into the blood, thereby resulting in high serum bilirubin level. Therefore, severe hyperbilirubinemia often indicates serious liver injury.\[21,22\]

Serum creatinine is the final product of creatine metabolism, which is excreted through the kidney. Serum creatinine is often used as a major clinical marker of renal function. Studies have shown that patients with severe chronic

### Table 3: Comparison of general conditions and laboratory tests at initial stage of survivors versus that of nonsurvivors in DILI with SJS/TEN

| Variable                        | Nonsurvivors (n=9) | Survivors (n=31) | t/Z/χ² | P     | OR    | 95% CI |
|---------------------------------|-------------------|-----------------|--------|-------|-------|--------|
| Age (years)                     | 58.56±23.30       | 46.03±20.48     | 0.895  | 0.125 |       |        |
| Male/female                     | 7/2               | 18/13           | 1.157  | 0.440 |       |        |
| Time‡                          | 10.56±5.27        | 9.13±3.71       | 0.748  | 0.631 |       |        |
| Pre-existing liver disease      | 3                 | 3               | 3.061  | 0.115 |       |        |
| Chronic underlying disease†     | 6                 | 19              | 0.086  | 0.769 |       |        |
| WBC count (10⁹/L)               | 12.29±3.11        | 11.69±7.83      | 1.202  | 0.111 |       |        |
| HB count (g/L)                  | 101.00±29.18      | 120.80±21.97    | -2.21  | 0.033 |       |        |
| RBC count (10⁹/L)               | 3.66±1.18         | 4.07±0.48       | -1.582 | 0.122 |       |        |
| AST (U/L)                       | 232.07±237.43     | 135.43±118.76   | 0.710  | 0.695 |       |        |
| ALT (U/L)                       | 347.16±265.11     | 299.38±259.77   | 0.994  | 0.277 |       |        |
| g-GT (U/L)                      | 343.09±186.68     | 217.57±217.21   | 1.240  | 0.092 |       |        |
| Total bilirubin (mmol/L)        | 60.58±60.03       | 21.13±19.07     | 1.533  | 0.018 |       |        |
| Direct bilirubin (mmol/L)       | 28.45±20.84       | 12.72±15.09     | 1.032  | 0.237 |       |        |
| Indirect bilirubin (mmol/L)     | 25.89±60.18       | 7.79±5.25       | 1.335  | 0.057 |       |        |
| ALP (U/L)                       | 296.00±150.74     | 199.39±111.67   | 2.110  | 0.042 |       |        |
| Serum albumin (g/L)             | 31.68±3.52        | 32.59±4.50      | -0.556 | 0.582 |       |        |
| CRP (mg/L)                      | 104.35±108.09     | 23.13±22.56     | 1.335  | 0.057 |       |        |
| Serum creatinine (mmol/L)       | 298.31±271.06     | 104.65±84.93    | 1.382  | 0.044 |       |        |
| Eosinophil (10⁹/L)              | 1.13±2.18         | 0.61±0.92       | 1.193  | 0.116 |       |        |
| Lymphocyte (10⁹/L)              | 2.74±1.97         | 3.52±3.86       | 0.521  | 0.696 |       |        |

†Time elapsed from the occurrence of cutaneous involvement to diagnosis. §Chronic underlying disease included diabetes, hypertension, and hyperlipidemia. WBC: White blood cell; HB: Hemoglobin; RBC: Red blood cell; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; g-GT: G-glutamyltransferase; ALP: Alkaline phosphatase; CRP: C-reactive protein. P values in bold are statistically significant.

### Table 4: Multivariate logistic regression analysis of clinical prognostic markers of DILI in patients with SJS/TEN

| Variable                     | B     | S.E.  | Wald  | P    | OR   | 95% CI      |
|------------------------------|-------|-------|-------|------|------|-------------|
| HB count (10¹²/L)            | 0.092 | 0.051 | 3.232 | 0.072| 1.097| 0.992~1.213 |
| ALP (U/L)                    | 0.017 | 0.011 | 2.224 | 0.136| 1.017| 0.959~1.040 |
| Total bilirubin (mmol/L)     | -0.123| 0.061 | 4.133 | <0.05| 0.884| 0.785~0.996 |
| Serum creatinine (mmol/L)    | -0.012| 0.005 | 5.406 | <0.05| 0.988| 0.978~0.998 |
liver disease have a higher rate of kidney injury, with poor prognosis.[23] In this study, high serum creatinine level was significantly associated with poor prognosis of DILI in patients with SJS/TEN, which may be related to kidney injury, severely affecting the drug metabolism and excretion. The concurrent injury of liver, kidney, and extensive skin seriously affects the physical functions of the patients, and may trigger a series of physiological dysfunctions leading to adverse prognosis.

**Conclusion**

DILI is often associated with SJS/TEN. The patients with SJS/TEN have a higher risk of liver injury due to xanthine oxidase inhibitors, dibenzazepines, and TCM. Pre-existing liver disease, diabetes, and hyperlipidemia are independent risk factors for DILI in patients with SJS/TEN. Serum total bilirubin and creatinine levels should be closely monitored when patients with SJS/TEN have developed liver injury.

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**Conflicts of interest**

There are no conflicts of interest.

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