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Commentary

Increased attention to women with drug-induced liver injury: Risk factors and early intervention☆

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A B S T R A C T

A recent study by Xiong Yu-Ting and colleagues has unveiled the clinical characteristics and risk factors of acute drug-induced liver injury (DILI). Upon reading the article, we found that there are some differences between female and male patients with DILI in terms of clinical and pathological features, especially in the number of patients, the degree of liver inflammation, and the risk of autoimmune liver disease. Therefore, it is necessary to pay attention to female patients with DILI and their outcomes, and to intervene appropriately in advance. This article analyzes the reasons for the differences between female and male patients with DILI and makes recommendations for patient prognosis.

We recently read with great interest an article by Xiong et al. [1], which examined the clinical characteristics and risk factors for significant liver inflammation in patients with acute drug-induced liver injury (DILI). The study found that female sex, high body mass index (BMI), elevated total bilirubin, and reduced prothrombin activity were linked to severe liver inflammation. These findings provide valuable insights into the prognosis and follow-up of these patients. The article highlighted that female DILI patients had a higher prevalence of significant liver inflammation in the context of DILI compared with male patients. Additionally, women with severe liver inflammation were at a higher risk of developing autoimmune conditions during follow-up. The transformation of the clinical pattern from hepatocellular injury to cholestatic injury was also more prominent in female patients [1]. Based on these findings, several critical issues regarding female DILI patients merit further discussion.

First, why is the proportion of female DILI patients higher? This can largely be attributed to sex differences in drug sensitivity and metabolism. Although there is no definitive evidence that women are at higher risk for DILI from all drugs, they are more susceptible to certain medications such as minocycline and nitrofurantoin [2]. This increased susceptibility may result from the influence of sex hormones on immune responses and inflammation in women [3], potentially triggering drug-induced autoimmune reactions and liver injury [2]. Variations in specific human leukocyte antigen (HLA) genotypes may also increase sensitivity to drug reactions in women. For example, people carrying the HLA-B5701 genotype have a significantly increased risk of DILI when using flucloxacillin, and this risk is more pronounced in women [4]. Additionally, differences in gastrointestinal flora, body fat content, liver enzyme activity, and renal clearance between men and women may result in greater drug accumulation, higher blood concentration, and prolonged duration of action in women, leading to a higher incidence of adverse reactions [5]. Finally, differences in behaviors, lifestyle, and comorbidities between sexes may also play a role in the occurrence of DILI.

Second, the high incidence of DILI and its outcomes in overweight women is another key area of focus. While there is no evidence that being overweight increases overall susceptibility to DILI, it may increase the risk of DILI from specific drugs, such as tamoxifen and methotrexate [6]. Obesity is closely associated with metabolic dysfunction-associated fatty liver disease, where increased fat content in the liver can promote inflammation and fibrosis, thereby increasing the risk of DILI [7]. Therefore, lifestyle interventions, such as dietary management and increased physical activity, are critical for overweight women at risk for DILI, as is active management of metabolic dysfunction-associated fatty liver disease and avoidance of potentially hepatotoxic medications. In cases where hepatotoxic drugs cannot be avoided, we recommend

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regular bi-weekly assessments of liver function and coagulation status in these patients and, when necessary, the use of hepatoprotective agents, dose adjustments, or timely drug cessation. Treatment decisions should be individually tailored, taking into account the patient's overall health, the hepatotoxic profile of the medication, and the patient's therapeutic response.

Additionally, DILI with autoimmune features (DI-ALH) is relatively common among female DILI patients. Of the 157 patients with DILI observed by Xiong et al., all cases of autoimmune liver disease occurred in women [1]. Sex-based metabolic differences may influence the production of metabolites, and an enhanced immune response in women may recognize these metabolites as neoantigens, triggering immune-mediated liver injury [8]. Differentiating DI-ALH from autoimmune hepatitis (AIH) is challenging in practice, as liver biopsy may not conclusively distinguish between the two. Unlike AIH, most DI-ALH patients do not relapse following discontinuation of glucocorticoid therapy within 1–6 months, which is a key distinguishing factor [9]. However, a minority of patients with DI-ALT may follow a natural course similar to AIH, even after discontinuation of the suspected drug that triggered the autoimmune response. Therefore, long-term follow-up is necessary for these patients, as well as close monitoring of liver function to adjust treatment as needed. It is worth noting that there are currently no guidelines for the management of DI-ALH, and treatment decisions are often guided by case reports or expert opinions, with a preference for short-term corticosteroids or immunosuppressants [2]. A long-term follow-up study indicated that the recurrence rate of DI-ALT increases over time, reaching 50% after 4 years of follow-up [10]. Thus, it is important to extend the follow-up period as much as possible. We recommend follow-ups at 2 weeks, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months after a definitive diagnosis, and annually thereafter for 5 years.

In conclusion, it is essential to closely monitor liver function in women, particularly overweight women, when prescribing drugs with reported DILI risk. For overweight female DILI patients, timely lifestyle interventions and management of metabolic dysfunction-associated fatty liver disease are crucial for reducing liver damage and improving liver function. For patients with DILI accompanied by autoimmune features, long-term follow-up is necessary to adequately differentiate the disease from AIH and adjust treatment plans accordingly. In the future, larger prospective studies are needed to further refine the natural history of DILI in women and to explore the pathophysiological mechanisms underlying the heterogeneity of outcomes between men and women, which could lead to improved treatment options for DILI patients. For DI-ALH, the development of specific biomarkers or diagnostic tools, potentially utilizing immune cell phenotyping, may aid in diagnosis.

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CRediT authorship contribution statement

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Declaration of competing interest

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