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Drug-induced liver injury in children: A nationwide cohort study from China

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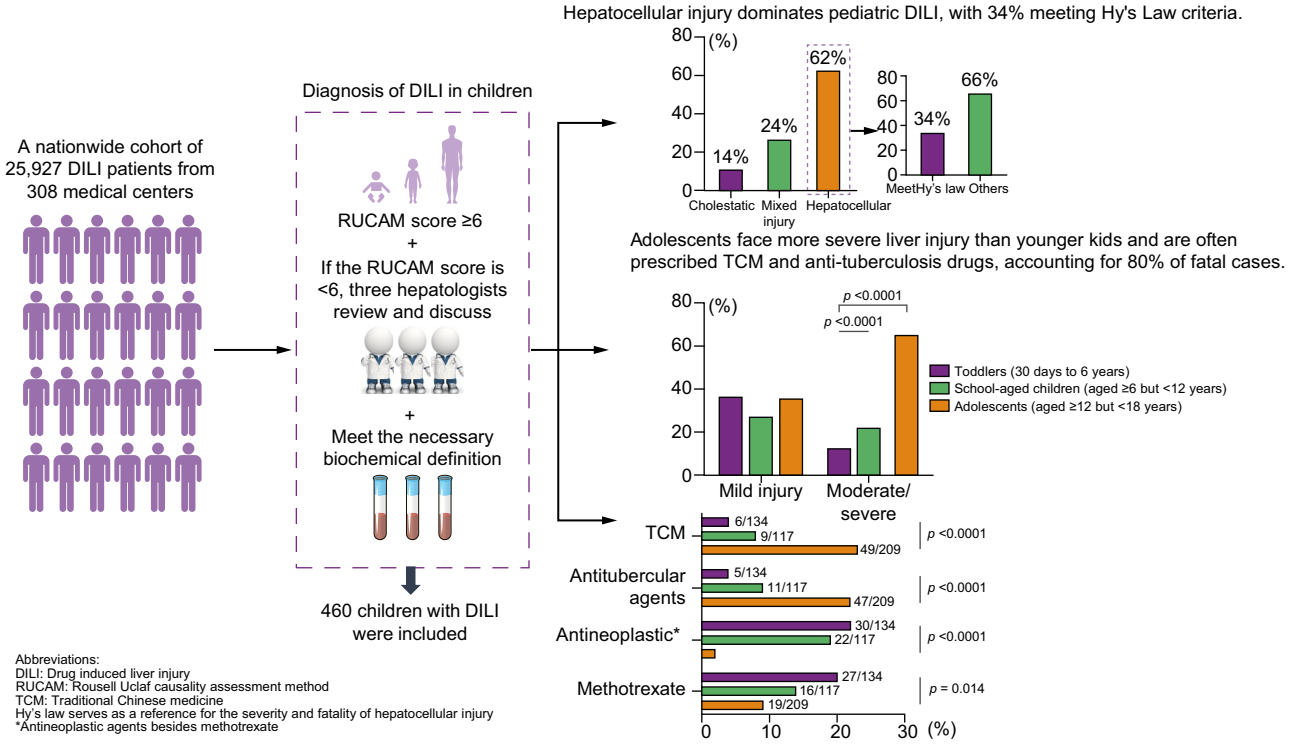
Graphical abstract



Highlights:

- Out of 25,927 Chinese DILI cases nationwide, we identified 460 children with high-confidence DILI as defined by EASL.
- Hepatocellular injury was the predominant clinical phenotype, with 30% meeting Hy's Law.
- Antineoplastics, antimicrobials, and traditional Chinese medicines were the leading causes of pediatric DILI.
- Children with more severe injuries were often prescribed anti-tuberculosis medications and traditional Chinese medicines.
- Compared to younger children, severe liver toxicity was more common in adolescents.

Impact and implications:

Drug-induced liver injury, a poorly understood yet serious cause of pediatric liver disease, encompasses a spectrum of clinical presentations, ranging from asymptomatic liver enzyme elevation to acute liver failure. This retrospective study, utilizing a large Chinese cohort of pediatric liver injury cases from 308 centers nationwide, characterized the major clinical patterns and suspected drugs in detail, revealing that adolescents are at a greater risk of severe liver injury compared to younger children. Vigilant care and careful surveillance of at-risk pediatric patients are crucial for physicians, researchers, patients, caregivers, and policymakers. Additional multicenter prospective studies are needed to evaluate the risk of hepatotoxicity in outpatients and hospitalized pediatric patients.

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Research article

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Drug-induced liver injury in children: A nationwide cohort study from China

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Background & Aims: Currently, there is limited knowledge on the clinical profile of drug-induced liver injury (DILI) in Chinese children. We aimed to assess the clinical characteristics, suspected drugs, and outcomes associated with pediatric DILI in China.

Methods: This nationwide, multicenter, retrospective study, conducted between 2012 and 2014, analyzed 25,927 cases of suspected DILI at 308 medical centers using the inpatient medical register system. Utilizing the Roussel Uclaf causality assessment method score, only patients with scores ≥6 or diagnosed with DILI by three experts after scoring <6 were included in the analysis. Among them, 460 cases met the EASL biochemical criteria. The study categorized children into three age groups: toddlers (≥30 days to <6 years old), school-age children (6 to <12 years old), and adolescents (12 to <18 years old).

Results: Hepatocellular injury was the predominant clinical classification, accounting for 63% of cases, with 34% of these cases meeting Hy's law criteria. Adolescents comprised the majority of children with moderate/severe DILI (65%). Similarly, adolescents faced a significantly higher risk of severe liver injury compared to younger children (adjusted odd ratios 4.75, $p = 0.002$). The top three most frequently prescribed drug classes across all age groups were antineoplastic agents (25.9%), antimicrobials (21.5%), and traditional Chinese medicine (13.7%). For adolescents, the most commonly suspected drugs were antitubercular drugs (22%) and traditional Chinese medicine (23%).

Conclusion: Adolescents are at a greater risk of severe and potentially fatal liver injury compared to younger children. Recognizing the risk of pediatric DILI is crucial for ensuring safe medical practices.

Introduction

Drug-induced liver injury (DILI) remains a poorly understood but serious cause of pediatric liver disease. Pediatric DILI encompasses a spectrum of clinical presentations, ranging from asymptomatic elevations in liver enzymes to severe hepatotoxicity leading to acute liver failure. The severity can vary widely, with some cases resolving upon discontinuation of the offending medication, while others progress to life-threatening complications. The etiology of pediatric DILI is diverse, involving numerous medications, herbal supplements, and alternative therapies. Identifying the culprit agent and understanding its mechanism of hepatotoxicity is essential for proper management. Additionally, age-related differences in pharmacokinetics and drug metabolism contribute to the unique clinical characteristics observed in pediatric patients.[1] The distinct pharmacokinetics and drug-metabolizing enzyme profiles of pediatric patients, owing to their immature systemic development, render them potentially more susceptible to DILI than adults.[2,3] Furthermore, children are often underrepresented in clinical trials for new drugs, leading to limited monitoring for hepatotoxicity. In recent years, there has been a notable shift in the profile of suspected drugs, with newly identified plant extracts, immune checkpoint inhibitors, and COVID-19 vaccines emerging as potential culprits.[4] Consequently, the risk of DILI in children may be heightened in routine clinical practice.

Idiosyncratic DILI and acetaminophen hepatotoxicity stand as primary drivers behind severe live injury and acute liver failure (ALF) in children in Western populations.[1,5] In the United States, antimicrobial agents and central nervous system drugs are identified as the primary culprits of pediatric liver injury. Meanwhile, in India, complementary and alternative medicine, along with antitubercular drugs, take precedence as the leading

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suspects in pediatric DILI.[6] A single-center study from China indicated antibiotics as the most suspected agents for pediatric DILI within a cohort of 69 cases.[7]

To date, there remains limited evidence regarding the clinical spectrum and severity of pediatric DILI in China. This study was extracted from the largest nationwide cohort of DILI cases, aiming to comprehensively assess the clinical characteristics, etiology, and severity of pediatric DILI, stratified by sex and age. The aim was to identify high-risk groups of pediatric DILI in clinical practice and provide meaningful insights for interventions and treatment strategies.

Patients and methods

Data sources and collection

The pediatric DILI study is a component of a national retrospective series comprising records from 25,927 DILI hospitalizations documented in the inpatient medical registry.[8] The study period spanned from 2012 to 2014, commencing in 2015 under Ethical No: 2015-040K, and involved 308 centers across China and encompassed case identification and data cleaning activities until 2017. To ensure diagnostic accuracy, each center assessed patients with DILI using the updated Roussel Uclaf causality assessment method (RUCAM) scores.[9] Patients with scores ≥6 were included, while those with scores <6 were discussed by three hepatologists. Ultimately, patients with suspected DILI had to meet minimum laboratory criteria for inclusion.[4,10] The first epidemiological study based on this database was published in 2019, providing detailed insights into the methodology and diagnostic approach.[8]

Study participants

Inclusion criteria for this study were as follows: 1) the age at which DILI occurred was within the pediatric range (30 days to <18 years old). Neonates within 30 days of birth were excluded from this study, considering the physiological jaundice commonly observed in newborns. 2) All liver-related clinical test results had to meet the criteria outlined in the 2019 EASL Clinical Practice Guidelines for DILI.

From the initial pool of 25,927 DILI cases, we excluded adults, cases with missing information, and those not meeting the 2019 EASL criteria, resulting in a final sample of 460 children for this study (Fig. S1). We created specialized, standardized case report forms for all cases. Hospitalization information of patients was extracted from electronic medical records, including: 1) demographic information (such as gender, age, and BMI); 2) history of previous illnesses, allergies, and surgeries; 3) duration of hospitalization, latency period, and recovery time; 4) clinical manifestations, symptoms and time of presentation and recovery; 5) results of laboratory serological tests, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamyl transferase (GGT), total bilirubin (TBIL), direct bilirubin, albumin (ALB), total protein, prothrombin time (PT), prothrombin time-international normalized ratio (PT-INR) and autoantibody tests; 6) medication history associated with DILI, including specific categories and duration of implicated drugs; 7) severity of disease, clinical outcomes, and prognosis; 8) findings to rule out other causes of liver injury.

Diagnosis and clinical patterns of pediatric DILI

Children were divided into three age groups: toddlers, aged from 30 days to 6 years; school-aged children, aged ≥6 and <12 years; and adolescents, aged ≥12 but <18 years.[11] As per the 2019 EASL Clinical Practice Guidelines,[10] the diagnosis of DILI includes meeting one of the following thresholds: 1) ALT ≥5 × the upper limit of normal (ULN); 2) ALP ≥2 × ULN, accompanied by elevated GGT and absence of known bone disease; and 3) ALT ≥3 × ULN concomitant with TBIL >2 × ULN. The clinical pattern of DILI was classified based on the "R" value. The "R" value is calculated as R = (ALT/ULN)/(ALP/ULN). An ALT ≥5 × ULN or R ≥5 was termed "hepatocellular," ALP ≥2 × ULN or R ≤2 was "cholestatic," while 2< R <5 was classified as "mixed."

Latency refers to the period from initiation of implicated drug therapy to the first detection of abnormal serum liver biochemical parameters (ALT, AST, ALP, or TBIL).

Severity and clinical outcomes

Using the severity classifications of the International DILI Expert Working Group,[12] DILI is categorized as mild, moderate, severe, and fatal/transplant. Mild DILI was defined as ALT ≥5x or ALP ≥2x and TBIL <2 × ULN; moderate DILI as ALT ≥5x or ALP ≥2x and TBIL ≥2 × ULN, or symptomatic hepatitis; severe DILI as moderate criteria alongside 1) INR ≥1.5, or 2) ascites or hepatic encephalopathy, with a duration without cirrhosis of ≤26 weeks, and another organ failure due to DILI.

Hy's Law serves as a reference for determining the morbidity and mortality of hepatocellular type.[13] It is defined as 1) serum ALT or AST >3 × ULN and >2 × ULN elevation in TBIL; 2) absence of cholestasis (as evidenced by elevated ALP); 3) absence of viral hepatitis or other previous or acute liver diseases driving the rise in ALT, AST or TBIL, or other drugs that could cause visible damage.

Pediatric acute liver failure is defined as acute-onset liver disease without evidence of chronic liver disease or biochemical evidence of severe liver injury, resulting in coagulopathy that is unresponsive to vitamin K correction. This is indicated by a prothrombin time ≥15 s or an INR ≥1.5 with encephalopathy, or a prothrombin time ≥20 s or an INR ≥2 with or without encephalopathy.[1]

Statistical analysis

All statistical analyses were conducted using SAS 9.3 for Windows (SAS Institute Inc., Cary, NC, USA). For continuous variables, the Mann-Whitney *U* test or Kruskal-Wallis test was appropriately utilized because the dataset did not follow a normal distribution. Descriptive statistics are presented as median (IQR) or 95% CIs. The chi-square test or Fisher's exact test was appropriately used for categorical variables to compare differences between test groups.

Univariable and multivariable logistic regression analyses were performed to assess the odds ratios (ORs) with 95% CIs of factors potentially linked to the development of moderate to severe DILI. Variables known to be associated with these outcomes based on previous or with a univariable ORs of p <0.10 were included in the multivariable model. Statistical significance was set at a two-tailed p <0.05. Graphs were plotted using GraphPad prism 80.0.

Results

Demographic and clinical characteristics of children with DILI

Among the 460 children eventually enrolled in this study with DILI, 259 were boys, constituting 56.3%, slightly outnumbering girls (43.7%). Adolescents comprised the largest proportion (45.4%), followed by toddlers (29.1%) and school-aged children (25.4%). The detailed distribution of our cohort by sex and age is presented in Table S1. The clinical classification of DILI was predominantly hepatocellular injury (62.6%), followed by the mixed type (26.7%), and the cholestatic type (10.7%). Approximately 34.1% of children with hepatocellular injury met Hy's law criteria. During hospitalization and treatment, 78 patients developed jaundice. Among the ten pediatric DILI patients with severe prognoses, eight progressed to ALF, two died, and one of the mortalities was attributed to DILI-related ALF, resulting in a mortality rate of 0.4%. A notable 96.7% of patients had a maximum serum ALT test of >5 × ULN, compared to 61.7% at admission. Additionally, the peak serum test results revealed 60.4% and 240.0% of patients exceeded 5 × ULN for AST and TBIL, respectively (Table 1).

Comparison of clinical parameters for children with DILI of different severity, sex, and age

Following the severity definition set by the International DILI Expert Working Group,[12] 291 of our patients met the criteria, with 206 classified as mild and 85 as moderate or higher. We investigated differences between these groups (Table 2). Boys

Table 1. Demographic and clinical characteristics of 460 pediatric DILI cases.

Variable	Number	%	95% CI
Sex			
Boys	259	56.3	[51.7-60.8]
Girls	201	43.7	[39.2-48.3]
Age (year)			
Toddlers (≥30 days and <6 years old)	134	29.1	[25.2-33.4]
School-aged children (≥6 and <12 years old) years)	117	25.4	[21.7-29.6]
Adolescents (≥12 and <18 years old)	209	45.4	[40.9-50.0]
Clinical types			
Hepatocellular injury (R ≥5)	258	62.6	[57.9-67.2]
Conform to Hy's law	88	34.1	[28.6-40.1]
Others	170	65.9	[59.9-71.4]
Cholestatic injury (R ≤2)	44	10.7	[8.1-14.0]
Mixed injury (2<R <5)	110	26.7	[22.7-31.2]
Initial serum ALT (U/L)			
≥5 × ULN	284	61.7	[57.2-66.1]
≥3 × ULN and <5 × ULN	54	11.7	[9.1-150.0]
<3 × ULN	122	26.5	[22.7-30.7]
Peak serum ALT (U/L)			
≥5 × ULN	445	96.7	[84.7-98.0]
≥3 × ULN and <5 × ULN	12	2.6	[1.5-4.5]
<3 × ULN	3	0.7	[0.2-1.9]
Initial serum AST (U/L)			
≥5 × ULN	135	29.3	[25.4-33.7]
≥3 × ULN and <5 × ULN	72	15.7	[12.6-19.3]
<3 × ULN	253	550.0	[50.4-59.5]
Peak serum AST (U/L)			
≥5 × ULN	278	60.4	[55.9-64.8]
≥3 × ULN and <5 × ULN	90	19.6	[16.2-23.4]
<3 × ULN	92	20.0	[16.6-23.9]
Initial serum TBIL (μmol/L)			
≥10 × ULN	39	8.7	[6.4-11.7]
≥5 × ULN and <10 × ULN	41	9.2	[6.8-12.2]
≥2 × ULN <5 × ULN	31	6.9	[4.9-9.7]
<2 × ULN	336	75.2	[71.0-78.9]
Peak serum TBIL (μmol/L)			
≥10 × ULN	62	13.9	[11.0-17.4]
≥5 × ULN and <10 × ULN	45	10.1	[7.6-13.2]
≥2 × ULN <5 × ULN	44	9.8	[7.4-13.0]
<2 × ULN	296	66.2	[61.7-70.4]
Presentation of clinical jaundice			
Yes	78	17.0	[13.8-20.7]
No	382	83.0	[79.3-86.2]
Fatal outcomes			
Acute liver failure	8	1.7	[0.9-3.4]
Death	2	0.4	[0.1-1.6]
DILI had a primary role	1	50	[2.6-97.4]
DILI had no role	1	50	[2.6-97.4]

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TBIL, total bilirubin; ULN, the upper limit of normal. Data are presented as n (%) and corresponding 95% CIs, where n is the actual number with available data. Pearson chi-square test.

Table 2. Comparison of clinical characteristics between pediatric DILI cases with mild and moderate/severe manifestations.

Characters	Total (N = 291)	ALT ≥5x ULN or ALP ≥4x ULN and TBIL <2x ULN (Mild, n = 206)	ALT ≥5x ULN or ALP ≥4x ULN and TBIL ≥2x ULN and life-threatening DILI (≥Moderate, n = 85)	*p* value
Sex, n (%)				
Boys	171 (60.2)	124 (61.7)	47 (56.6)	0.428
Girls	113 (39.8)	77 (38.3)	36 (43.4)	
Age (year), median (IQR)				
Toddlers (≥30 days and <6 years old)	86 (29.6)	75 (36.4)	11 (12.9)	**<0.0001**
School-aged children (≥6 and <12 years old)	76 (26.1)	57 (27.7)	19 (22.4)	
Adolescents (≥12 and <18 years)	129 (44.3)	74 (35.9)	55 (64.7)	
BMI (kg/m^2), median (IQR)	19.1 (16.9, 20.8), n = 129	19.0 (17.2, 20.9), n = 73	19.2 (16.7, 20.8), n = 56	0.640
Duration of using implicated agent (days), median (IQR)	9 (5, 31), n = 151	9 (4, 21), n = 100	11 (7, 50), n = 51	**0.019**
Latency (days), median (IQR)	17 (8, 53), n = 158	13 (7, 37), n = 101	26 (15, 67), n = 57	**0.0005**
Hospitalization (days), median (IQR)	14 (7, 22), n = 291	12 (5, 19), n = 206	18 (12, 28), n = 85	**<0.0001**
Pattern of liver injury, n (%)				
Hepatocellular injury (R ≥5)	158 (620.0)	103 (58.9)	55 (68.8)	0.209
Cholestatic injury (R ≤ 2)	35 (13.7)	28 (160.0)	7 (8.7)	
Mixed injury (2<R <5)	62 (24.3)	44 (25.1)	18 (22.5)	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; DILI, drug-induced liver injury; TBIL, total bilirubin; ULN, the upper limit of normal.
Data are presented as the median (IQR) or n (%), n, where n is the actual number with available data. Pearson chi-square test for categorical variables, Student's *t* test for variance, or Wilcoxon rank-sum for continuous variables. Values in bold denote statistical significance.

constituted the majority in both categories (61.7% mild and 56.6% >moderate). The mild group predominantly comprised toddlers (36.4%), whereas adolescents were predominant in the moderate/severe group (64.7%). The moderate/severe group often exhibited a longer latency period compared to the mild group. In children with mild DILI, the median latency was 13 days, whereas it was 26 days in the moderate/severe group ($p = 0.0005$). Gastrointestinal symptoms were prevalent in both groups; however, the mild group showed a higher incidence of fever (22.8% *vs* 5.2%, $p = 0.002$). The moderate/severe group displayed more severe symptoms such as jaundice (62.3% *vs* 10.1%, $p < 0.0001$), hepatic encephalopathy (5.9% *vs* 0%, $p = 0.0005$), and organ functional disorders (60.0% *vs* 0.5%, $p = 0.004$) (Table S2). The definitions of organ dysfunction were based on diagnoses recorded within the registry systems of participating centers, encompassing respiratory, renal, cerebral, and circulatory failure,[14] but excluding liver failure.

Liver function indicators were stratified by sex and age to profile DILI characteristics. While there was no sex difference in liver test outcomes, age groups exhibited variations. Adolescents had higher levels of GGT ($p < 0.0001$), TBIL ($p < 0.0001$), PT ($p = 0.042$), and PT-INR ($p = 0.0001$) compared to other age groups and also exhibited a noticeably longer latency period ($p = 0.0051$). Although ALT and AST trends were higher in adolescents without statistical differences, ALP ($p = 0.0006$) and ALB ($p = 0.0009$) were significantly lower (Fig. 1).

Suspected drugs in children with DILI

After categorizing drugs and formulations for 460 pediatric DILI cases, 78.9% received single drug treatments, while 21.1% had combination therapies. The top three single drugs were antineoplastics (25.9%), antimicrobials (21.5%), and traditional Chinese medicine (TCM) (13.7%). Methotrexate was the most frequently administered antineoplastic, representing 13.5% of cases, closely followed by antitubercular drugs (13.9%). Other antimicrobials and non-steroidal anti-inflammatory drugs were each linked to over 30 reported cases, accounting for 7.6% and 6.5% of cases, respectively (Table S3).

In the case of single drugs, the mild DILI group exhibited a notably higher proportion of antineoplastic agent use, including both methotrexate and its alternatives, compared to the moderate/severe group ($p < 0.0001$). However, TCM use was more prevalent in the moderate/severe group ($p < 0.0001$).

Toddlers had a higher proportion of antineoplastic drug use, both methotrexate ($p = 0.014$) and others ($p < 0.0001$). They also took non-steroidal anti-inflammatory drugs more frequently than the other age groups ($p = 0.022$). Interestingly, adolescents presented a more diverse drug profile with a noticeable inclination towards multi-component antitubercular drugs ($p < 0.0001$) and compound TCM ($p < 0.0001$) compared to the other groups (Fig. 2B).

Clinical characteristics and suspected drug use in children with poor prognosis for DILI

Among the 460 pediatric patients with DILI, ten experienced adverse outcomes, with nine progressing to ALF. Two patients died, one due to complications from ALF. Ages ranged from 8 to 17, with adolescents (12-18 years old) being predominant (80%). Boys and girls were equally represented. 50% had taken antimicrobials (excluding antitubercular agents), 40% used

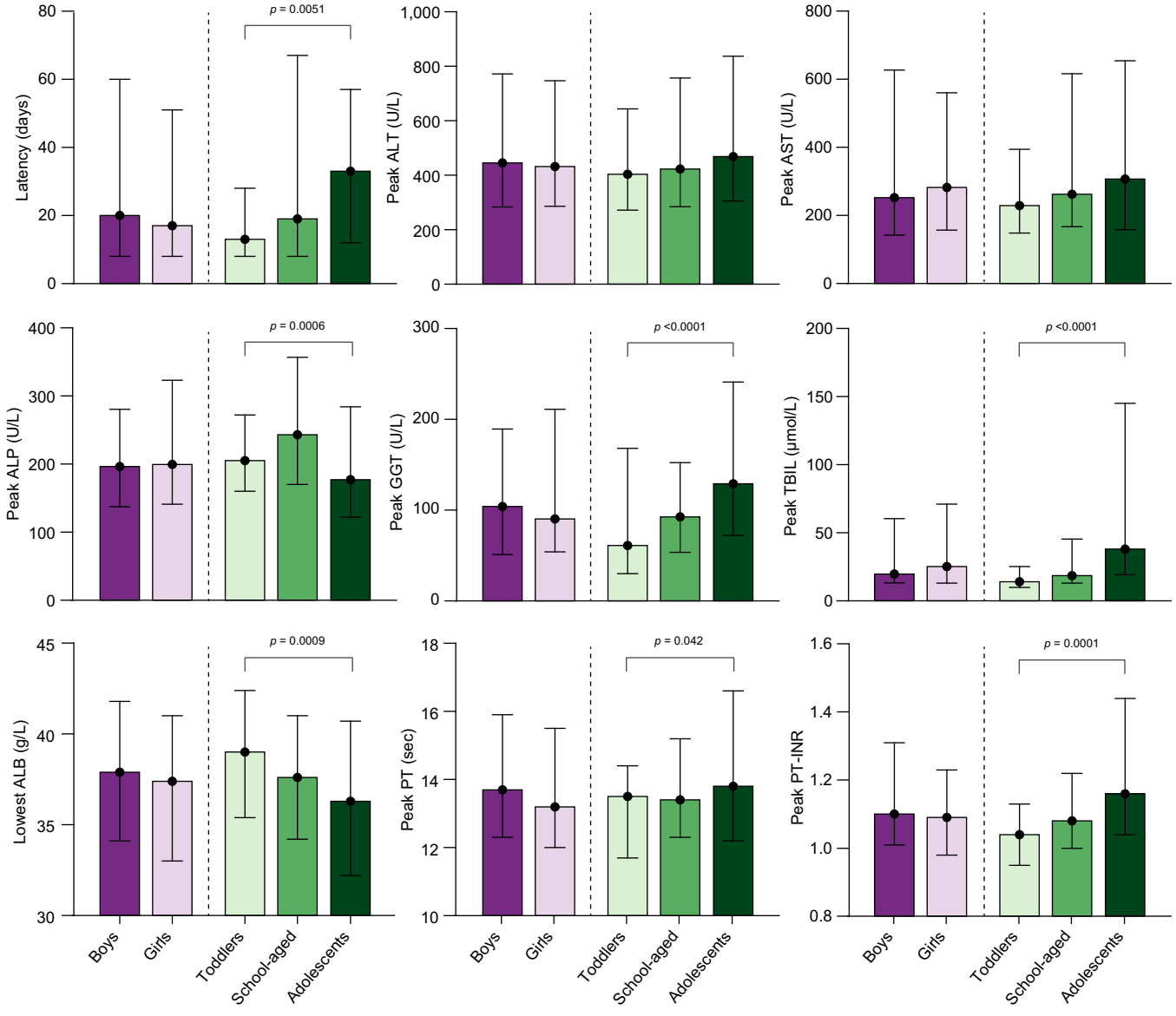

Fig. 1. Comparison of liver function tests in children with DILI, stratified by sex or age. Groups were shown as columns with median (IQR). Student's *t* test. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; GGT, gamma-glutamyltransferase; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; TBIL, total bilirubin.

acetaminophen, and 40% had TCM. Other drugs like antitubercular agents and antineoplastics might have also adversely impacted outcomes (Table 3).

Factors associated with the development of moderate/severe DILI

In multivariable analysis, adjusting for age, sex, latency, peak PT, INR, serum ALB, and creatinine levels, two factors were identified as associated with the progression to moderate/severe DILI: adolescence (≥12 and <18 years old) (adjusted odds ratio [aOR] 4.75; 95% CI 1.84-13.70; p = 0.002) and elevated peak PT (aOR, 1.25; 95% CI 1.12-1.42; p <0.001). When treating age as a continuous variable (Table S4), the results regarding factors associated with moderate/severe DILI remained consistent with the primary analysis.

Discussion

To our knowledge, this study represents the largest national cohort of pediatric DILI cases to date, encompassing a diverse demographic from 308 centers across the country.

We implemented extensive measures to ensure the reliability and accuracy of our DILI diagnoses:[8] children were included in the study only after a thorough evaluation using the RUCAM scale, coupled with expert review discussions, and meeting the necessary laboratory criteria (Fig. S1). Our stratified analysis revealed age-related severity differences in liver injury, with sex being irrelevant (Fig. 1; Table 2). Adolescents, compared to younger children, often experienced more severe liver injuries, accounting for 80% of fatal cases, and were commonly prescribed antitubercular drugs or TCM (Tables 2 and 3; Fig. 2). In this study, nearly 80% received a single drug, with the top

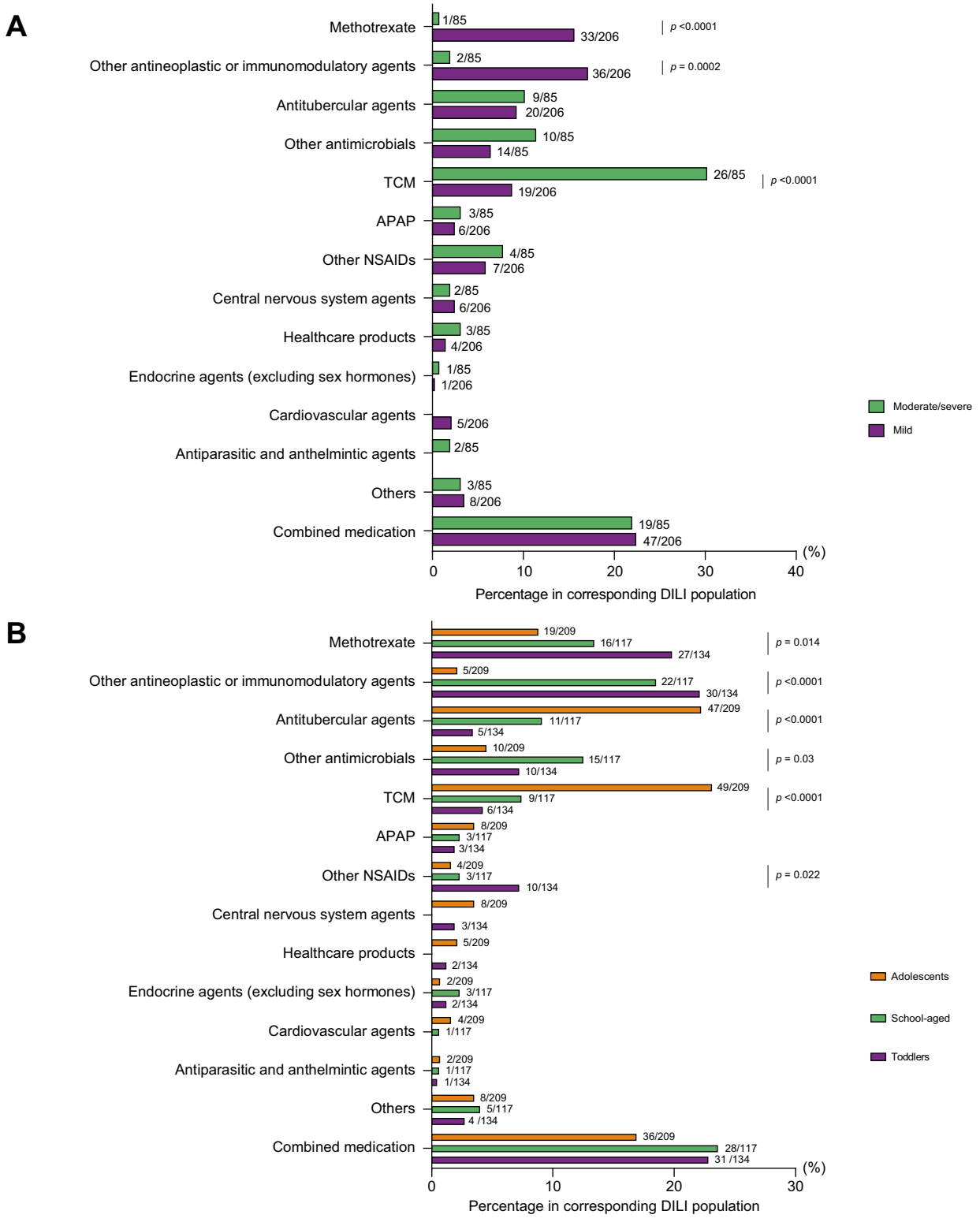

Fig. 2. Comparison of the characteristics of suspected drugs in children with DILI across severity levels or age groups. (A) Comparison of medication use in children with mild and moderate/severe DILI; (B) Comparison of medication use in children with DILI in toddlers, school-aged children, and adolescents. Other antimicrobials include antibacterial agents, antiviral agents, and antifungal agents, excluding antitubercular agents. Other NSAIDs refers to NSAIDs that exclude APAP. Endocrine agents exclude sex hormones. Others refer to other single medications with unclear classifications. Pearson chi-square test. APAP, acetaminophen; DILI, drug-induced liver injury; NSAIDs, non-steroidal anti-inflammatory drugs; TCM, traditional Chinese medicine.

Table 3. Specific information on pediatric DILI cases resulting in fatal outcomes (ALF and death).

NO.	Sex	Age	ALF/death	Implicated drugs	Peak TBIL (μmol/L)	Peak ALT (U/L)	Peak AST (U/L)	Peak ALP (U/L)	Peak GGT (U/L)	Peak PT (seconds)
007244	Boy	13	ALF	APAP + antimicrobials*	696.3	612.0	423.6	305.0	48.4	40.7
017145	Girl	17	ALF	Health care products	565.0	723.0	321.0	308.0	554.9	87.5
027378	Boy	17	ALF	Antitubercular agents + TCM	119.5	2,597.0	2,322.0	154.0	52.0	96.3
048033	Girl	8	ALF	†NSAIDs + APAP + antimicrobials	509.7	266.4	245.9	368.1	319.2	24.1
108065	Boy	17	ALF	APAP + TCM	411.3	2,295.0	739.0	457.7	123.0	24.9
288037	Girl	16	ALF	TCM	348.7	379.0	552.0	138.0	92.0	26.1
309267	Boy	12	ALF	Antimicrobials + digestive agents	190.7	1,922.0	1,420.0	378.0	137.0	19.2
309421	Girl	12	ALF	APAP	116.2	1,417.0	417.0	205.0	211.0	17.5
309142	Girl	16	ALF-related death	Antimicrobials + TCM	257.8	2,520.0	1,250.0	215.0	215.0	93.1
335009	Boy	10	Death	Antineoplastic agents + antimicrobials	17.4	264.0	82.0	122.0	82.0	13.9

ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APAP, acetaminophen; AST, aspartate aminotransferase; DILI, drug-induced liver injury; GGT, gamma-glutamyltransferase; PT, prothrombin time; TBIL, total bilirubin; TCM, traditional Chinese medicine.
*Antimicrobials include antibacterial agents, antiviral agents, and antifungal agents exclude antitubercular agents.
†NSAIDs refers to NSAIDs that exclude APAP. DILI, drug-induced liver injury; ALF, acute liver failure; APAP, acetaminophen; TCM, traditional Chinese medicine; NSAIDs, non-steroidal anti-inflammatory drugs. Descriptive statistics.

culprits being antineoplastics, antibiotics, and TCM. Methotrexate was the primary offender among antineoplastics for pediatric liver injuries (Fig. 2; Table S3). These insights provide an overview of pediatric DILI in China and aid in understanding DILI trends, high-risk subgroups, and suspect drugs.

For many years, the US FDA has utilized Hy's Law in clinical trials to identify drugs that may cause serious liver toxicity and predict the potential risk of severe liver injury or ALF.[15] In this study, the predominant clinical pattern of pediatric DILI (62.6%) was hepatocellular injury, and about one-third of children with hepatocellular injury met Hy's law criteria (Table 1). Furthermore, disease progression was observed in certain patients during the hospitalization period, with both ALT and TBIL levels significantly higher than the biochemical indicators at the time of admission, and even 1.7% of cases deteriorating into liver failure (Tables 1 and 2). These findings indicated that life-threatening liver injury can occur during the progression of the disease in pediatric DILI.

Data from the VigiBase global pharmacovigilance database indicates that children comprise 10% of all DILI cases, with adolescents being the predominant age group.[16] This finding is consistent with our results, where adolescents accounted for 45% of all pediatric cases (Table 1). We found that adolescents, in comparison to younger children, were more susceptible to severe liver injury, exhibiting clinical manifestations such as jaundice, hepatic encephalopathy, dysfunction, significantly elevated GGT and TBIL levels (all p <0.0001), and prolonged PT (p = 0.042) and INR (p = 0.0001) (Fig. 1). Additionally, adolescents had a higher prescription rate of antitubercular drugs or TCM (Fig. 2; Table 2; all p <0.0001). After further adjustment for age, sex, latency, peak PT, INR, ALB, and creatinine levels, we observed a higher risk of moderate/severe liver injury in adolescents compared to children younger than 12 (aOR 4.75, p = 0.002, Table 4). The severity of liver injury was found to be related to age, but not sex (Fig. 1). Data from Drug-Induced Liver Injury Network (DILIN), Spain, and Iceland revealed no significant sex differences in DILI risk, consistent with our findings.[17–20]

In adolescents, we have observed widespread use of TCM and antitubercular drugs, a trend that aligns with Asia's most common DILI triggers (Fig. 2; Table S3). TCM, deeply ingrained in numerous Asian cultures and increasingly popular in the West, presents a complex challenge due to its intricate composition.[8,21] Studies from DILIN in the US and Spain showed that herbal and dietary supplements can cause more severe liver injury compared to pharmaceuticals, with a higher likelihood of progressing to ALF.[22,23] A single-center study in China highlighted more severe liver injuries in pediatric DILI cases treated with TCM compared to pharmaceuticals.[7] In 2018, China's drug administration laid down comprehensive guidelines for TCM, aiming to better grasp its associated risks and establish a clear causative link to hepatotoxicity.[24]

In our study, the mortality rate for Chinese children with DILI was 0.4% (Table 1), notably lower than the 4% reported among American children. We attribute this difference to the predominant involvement of antineoplastic drugs in Chinese pediatric DILI cases. These drugs are frequently detected during regular follow-up appointments before causing severe liver injury, potentially diluting the ratio of severe adverse reactions. With advances in pediatric oncology, the 5-year survival rate for children and adolescents with cancer has significantly improved.[25] In 2021, guidelines recommended long-term

Table 4. Factors associated with developing moderate/severe (univariate and multivariable logistic regression).

Variable	Univariable OR (95% CI)	*p* value	Multivariable OR* (95% CI)	*p* value
Age (year)				
<12 years (toddlers and children)	Ref		Ref	
≥12 and <18 years (adolescents)	4.85 (2.81-8.60)	**<0.001**	4.75 (1.84-13.70)	**0.002**
Sex				
Girl	Ref		Ref	
Boy	0.96 (0.57-1.61)	0.876	0.80 (0.32-1.99)	0.627
Latency (days)	1.02 (1.00-1.05)	**0.042**	1.01 (0.98-10.03)	0.669
Peak PT	1.09 (1.03-1.17)	**0.009**	1.25 (1.12-1.42)	**<0.001**
Peak INR	1.05 (0.97-1.19)	0.300	1.00 (0.87-1.11)	0.939
Peak albumin (g/L)	0.94 (0.90-0.98)	**0.008**	1.00 (0.91-1.09)	0.971
Peak creatinine (μmol/L)	1.01 (1.00-1.02)	**0.020**	1.00 (0.99-1.01)	0.799

INR, international normalized ratio; OR, odds ratio; PT, prothrombin time.
Values in bold denote statistical significance.
*Adjusted for age, sex, latency, peak PT, peak INR, peak albumin, and peak creatinine.

monitoring of liver toxicity for tumor survivors treated with drugs such as methotrexate, thioguanine, and mercaptopurine.[26]

A previous study of 57 children with DILI from DILIN identified antibiotics and antiepileptic drugs as common causes of liver injury, with an increasing prevalence of herbal remedies.[27,28] In this study, the top three culprits in single drug treatments were antineoplastics, antibiotics, and TCM (Table S3). In 2021, the China National Adverse Drug Reactions Monitoring System reported 1,206 pediatric liver-related adverse drug events, primarily involving analgesic, antineoplastic, and immunomodulatory drugs.[29] Relying solely on spontaneous reporting, the monitoring system lacked uniform diagnostic criteria and access to children's clinical indicators, raising concerns about its reliability that require future verification.

This study boasts several strengths. This cohort represents the largest and most diverse pediatric DILI cohort in China to date. We ensured reliable DILI diagnoses in included patients through RUCAM scoring, evaluations by three clinical experts, and adherence to established biochemical standards from practice guidelines. Our comprehensive analysis covered demographic characteristics, dynamic changes in biochemical indicators, and outcomes during hospital stays, providing an in-depth assessment of potential suspect drugs, high-risk groups, and characteristics of patients with severe or fatal liver injuries. These results lay the groundwork for cautious medication use and hepatotoxicity monitoring in high-risk groups in future clinical practice.

This study has some limitations. The first is the potential for bias in the selection procedure. Although we had access to more demographic characteristics and clinical information, including clinical symptoms, biochemical parameters, and outcomes, they were primarily sourced from inpatient system reports from each hospital. The severity of disorders in inpatients tended to be higher than that of outpatients, resulting in the loss of some information on DILI cases with milder conditions among outpatients. Additionally, newborns younger than 30 days were excluded from the study to prevent physiological jaundice from interfering with assessing clinical patterns and severity. Consequently, some information about potentially harmful drugs in newborns may have been lost. Another limitation is the study period (2012-2014), which may not reflect the current trends in pediatric DILI. Although the first epidemiological study based on this database was published in 2019, the COVID-19 outbreak delayed the review process for this manuscript.[8,30] The authors, primarily from infectious diseases and hepatology departments, shifted their focus to combating the pandemic.[30] Despite this limitation, the database remains valuable, boasting the largest sample size and most comprehensive information on pediatric DILI in China to date, covering the entire country with robust diagnostic criteria. However, the low prevalence of DILI, especially in children, and the time-consuming nature of case collection and diagnosis necessitate further collaboration between multiple centers to confirm our findings in prospective studies.

In summary, our study highlights that adolescents face a higher risk of severe DILI, particularly among those using antitubercular drugs and TCM. Antineoplastic drugs, especially methotrexate, were the most suspected agents in pediatric liver injuries. We hope that these findings guide clinical practice, increase surveillance of high-risk children, and drive future in-depth studies to uncover early risk signals for hepatotoxicity, promoting personalized treatment and monitoring strategies through omics research.

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Abbreviations

ALB, albumin; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; aOR, adjusted odds ratio; AST, aspartate aminotransferase; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; GGT, gamma-glutamyltransferase; INR, international normalized ratio; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; RUCAM, Rousell Uclaf causality assessment method; TCM, traditional Chinese medicine; TBIL, total bilirubin; ULN, the upper limit of normal.

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Conflict of interest

The authors of this study declare that they do not have any conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: Rongtao Lai and Tao Shen. Data analysis: Rongtao Lai, Xinjie Li, Tao Shen, Xinrong Zhang, and Xi'an Han. Manuscript drafting: Rongtao Lai and Xinjie Li. Study supervision: Qing Xie, Chengwei Chen, Tao Shen, and Yimin Mao. Data collection, data interpretation, and final approval: All authors.

Data availability statement

Due to regulatory constraints, data will not be available publicly.

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Supplementary data

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