**Supplementary Methods**

**Diagnosis criteria for DILI**

DILI diagnosis was followed with the AGA DILI Guidelines issued in 20219. All those enrolled DILI patients must meet the causality criteria, as RUCAM score ≥ 6 points. Specifically, the included DILI patients met one of the following criteria: (1) serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥5 times the upper limit of normal (ULN); (2) serum alkaline phosphatase (ALP) ≥2 ULN; or (3) ALT or AST ≥3 times and simultaneous elevation of total bilirubin (TBil) concentration ≥2 ULN. If the baseline indices were abnormal, we used the baseline values to replace ULN.

**Inclusion and exclusion criteria of patients**

All study participants were older than 16 years of age and had follow-up visits over 12 months after DILI onset. In the Center 1 retrospective cohort, we screened DILI patients from the biofluid library, in accordance with the aforementioned DILI diagnosis criteria9. Each patient underwent follow-up visits over 12 months, in order to determine the duration of DILI. In the Center 2 prospective cohort, each patient was enrolled in accordance with the aforementioned DILI diagnosis criteria, signed the informed consent form, and had follow-up visits over 12 months, to determine the duration of DILI.

Patients with autoimmune, alcoholic, non-alcoholic or viral liver diseases and other competitive etiologies were excluded. Patients that did not meet the aforementioned DILI diagnosis criteria were excluded. Patients with systemic diseases affecting the liver (thyroid, heart disease, HIV infection) were excluded. Miscellaneous causes such as patients with alcohol intake over 40 g/day were excluded. Patients with a history of bone marrow or liver transplantation before DILI onset were excluded. Patients not having continuous follow-up visits over 12 months or where the DILI duration could not be determined were excluded.

**Non-targeted metabolome profiling**

The serum samples of DILI patients were stored at -80℃. The samples were removed and recovered under 4℃. 200μL samples were accurately measured and put into an EP tube. Thrice the amount of precooled methanol was added and diluted, then vortex blended and centrifuged at 12000 r/min for 10 min at 4℃. The supernatant was absorbed using 1mL injector, filtered using a 0.22μm membranee; the QC sample was prepared with a 10μL mixture of each sample.

The sample was sequenced randomly and 4 µL aliquot of each sample was injected into a ZORBOX RRHD C18 analytical column (2.1 mm i.d. × 100 mm, 1.8 µm i.d., Agilent Technologies, USA). The column temperature was maintained at 30℃. For the chromatography analysis, separation was achieved with a 25 min linear gradient with the mobile phases of solvent A (water spiked with 0.1% formic acid) and solvent B (acetonitrile spiked with 0.1% formic acid). The flow rate was set as 0.30 mL/min. The gradient was used as follows: a linear gradient of 100% A over initial-1.0 min, 100–60% A over 1.0–9.0 min, 60–10% A over 9.0–19.0 min, 10–0% A over 19.0–21.0 min, 100% B over 21.0–25.0 min. The eluent was directly introduced into the mass spectrometer. For mass spectrometry, an Agilent 6550 Q-TOF mass spectrometer with an electrospray ionization source (ESI) in both positive and negative mode, was used. The electrospray source parameters were fixed as follows: electrospray capillary voltage was 3.5 kV in negative ionization mode and 4 kV in positive ionization mode. The mass range was set from m/z 80 to 1000. Gas temperature was 225℃ in negative ionization mode and 225℃ in positive ionization mode. Gas flow was 13 L/min. Nebulizer was set to 20 pisg (negative)and 20 pisg (positive). Sheath gas temperature was 275℃ and sheath gas flow was 12 L/min. Nozzle voltage was 2000 V in both negative and positive mode. For internal mass calibration during the MS analysis, reference masses 121.0509 (Purine, [C5H4N4+ H]+) and 922.0098 (HP-0921, [C18H18O6N3P3F24+H]+) were used in positive mode, and 112.9856 (TFANH4, [C2H4O2NF3− NH4]−) and 1033.9881 TFANH4+ HP-0921, [C20H22O8N4P3F27− NH4]−) were used in negative mode.

**Metabolic pathway enrichment analysis on duration-related metabolites**

To further explore the biological mechanism of DILI chronicity, we screened the significantly differential metabolites associated with chronic DILI in Center 1, and validated the discriminative ability of them in Center 2. Criteria for significant differences between groups were a fold change (FC) value greater than 2 and a between-group T-test P value less than 0.05, combined with a VIP greater than 1, and |p (corr)| greater than 0.5 screening. We used PCDL software with the KEGG and HMDB databases to annotate significantly differential metabolites. And we binned all the annotated differential metabolites as the holistic metabolomic signature (HMS) associated with the duration of DILI. Then we screened out the most-associated metabolites as the metabolic fingerprint (MFP) for the liver injury duration of DILI by hierarchical cluster analysis and computed an eigenmetabolite (i.e., a value which is representative of MFP) by dimension reduction according to the methods in the literature14. We further explored the metabolic alteration and mechanisms involved in DILI chronicity by system biology-based pathway enrichment analysis.