Clinical Description: Severe Hepatotoxicity (Grade 3/4)

Synonyms: Severe Acute Liver Injury, Grade 3 or 4 Liver Toxicity, Severe Hepatitis (when meeting severity criteria).

1. Clinical Case Definition

Severe Hepatotoxicity is an acute, potentially life-threatening condition characterized by significant injury and inflammation of the liver parenchyma. This phenotype defines a state of severe liver impairment based on standardized laboratory parameters, irrespective of the underlying etiology (e.g., drug-induced, viral, autoimmune, ischemic).

The clinical presentation is highly variable. Patients may be asymptomatic, identified solely through routine laboratory monitoring. When symptoms occur, they are often non-specific, including fatigue, malaise, anorexia, nausea, and right upper quadrant discomfort. The development of jaundice or scleral icterus indicates significant hyperbilirubinemia. The pattern of liver injury identified through laboratory assessment (including AST, ALT, Alkaline Phosphatase, TBil) can be hepatocellular, cholestatic, or mixed.

This phenotype is strictly defined by the severity of the biochemical abnormalities, corresponding to **Severe (Grade 3) or Life-threatening (Grade 4)** toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) standards, based on the Upper Limit of Normal (ULN):

- **Grade 3 (Severe):** Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) >5.0–20.0 × ULN; OR Total Bilirubin (TBil) >3.0–10.0 × ULN.
- **Grade 4 (Life-threatening):** AST or ALT >20.0 × ULN; OR TBil >10.0 × ULN. Grade 4 may also be defined by clinical signs of acute liver failure, such as new-onset significant coagulopathy (e.g., elevated PT/INR) or hepatic encephalopathy, irrespective of the degree of LFT elevation.

2. Phenotype Scope & Granularity

- **Temporal Context:** Incident. Focuses on identifying the new onset of an acute episode of severe hepatotoxicity.
- **Severity:** Restricted to Severe (Grade 3) or Life-threatening (Grade 4) based on CTCAE laboratory or clinical criteria. This scope is not inclusive of mild (Grade 1) or moderate (Grade 2) toxicity.
- **Acuity / Chronicity:** Acute event. This scope is not inclusive of stable chronic liver disease or cirrhosis unless an acute, severe exacerbation meeting the laboratory criteria occurs.

- **Etiology:** Etiology-agnostic. This definition captures the state of severe liver injury regardless of the underlying cause.
- **Population Context:** General population, although the CTCAE criteria are most commonly applied in oncology, clinical trials, and severe adverse drug reaction monitoring.

3. Related Conditions & Scope Boundaries

This phenotype defines the severity of liver injury, not the cause. The following conditions are related but distinct in scope:

- **Mild or Moderate Hepatotoxicity (Grade 1/2):** Liver enzyme elevations that do not meet the criteria for Grade 3 or higher are not within the scope of this phenotype.
- **Chronic Liver Disease / Cirrhosis:** The stable, chronic state of liver disease is not within the scope of this acute phenotype. However, an acute-on-chronic event that meets Grade 3/4 criteria *is* within scope.
- **Isolated Hyperbilirubinemia (e.g., Gilbert's Syndrome):** Benign conditions causing elevated bilirubin without evidence of significant parenchymal injury or cholestasis are not within scope.

4. Key Complications & Common Comorbidities

This section differentiates the core phenotype from its common clinical consequences or associations.

- **Acute Liver Failure (ALF):** The primary and most severe complication, characterized by encephalopathy and coagulopathy, representing the extreme end of the Grade 4 spectrum.
- **Coagulopathy:** Impaired synthetic function of the liver leading to bleeding risk.
- **Hepatic Encephalopathy:** Neuropsychiatric abnormalities due to the liver's inability to detoxify blood.
- **Hepatorenal Syndrome:** Kidney failure developing secondary to severe liver disease.

5. Intended Data Sources

This clinical description is intended for building concept sets against real-world administrative claims, electronic health record (EHR) databases, and patient registries. The target data should be standardized to the OMOP Common Data Model. Examples of licensable data sources where this concept set would be applied include:

- **Optum®** (Clinformatics® Data Mart, SES, Pan-Therapeutic)
- **Merative™** (MarketScan® Commercial Claims and Encounters)
- **Veradigm** (Health Verity, Practice Fusion EHR)
- **IQVIA** (AmbEMR, PharMetrics Plus)

- **HealthVerity**