Clarifying Classification of Liver Injury in Electronic Data Sources

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• Consulting: none
Traditional Approach to Identifying DILI: Spontaneous Reporting of Cases

Development of DILI:

- Start Drug
- Identify Liver Injury
- Evaluate Causes of Liver Injury
- Confirm DILI Case
- Report DILI Case

Limitations:

- Missed Liver Injury
- Incomplete Evaluation
- Missed DILI Case
- Case Not Reported

Lack of Ascertainment of DILI Cases + Selection Bias

Electronic Health Data: Resources to Identify Liver Injury

Electronic Health Data

Electronic Medical Records
- Hospitals
- Health systems (e.g., VA system)
- General practices: CPRD, THIN (UK)

Administrative Databases
- US Medicaid, Medicare
- HMO networks

CPRD = Clinical Practice Research Datalink; THIN = The Health Improvement Network
Use of Electronic Health Data to Overcome Limitations of Spontaneous Reporting

• Systematic identification of liver injury = complete ascertainment of cases
  – Identify diagnoses, laboratory results, procedures

• Lack of selection bias

• Capture large numbers of cases

• Real-time monitoring for liver injury
Opportunities from Studying Liver Injury in Electronic Health Data

• Availability of controls:
  – Similarly exposed patients without liver injury

• Risk factors, outcomes of liver injury

• Compare incidence of liver injury in users of drugs

• Associations between drugs and liver injury

• Identify liver injury early after onset
Challenges to Use of Electronic Health Data to Evaluate Liver Injury

• Must identify diagnosis codes that have sufficient yield to be efficient
  – Consider: lab abnormalities, procedures

• Need for supplementary records to confirm validity

• Ascertained signals with minimal noise

Few database studies evaluated liver injury as outcome
Aim: Determine ability of ICD-9 diagnoses to identify severe liver injury (w/o regard for etiology) within FDA’s Mini-Sentinel Distributed Database

- **Sub-Aim 1**: Evaluate in members without pre-existing liver / biliary disease
- **Sub-Aim 2**: Evaluate in members with chronic liver disease
Study Design / Data Source

• Design: Cross-sectional analysis

• Source: FDA’s Mini-Sentinel Distributed Database*
  – Common data model: demographics, diagnoses, procedures
  – 5 data partners:
    • HMO Research Network
    • HealthCore, Inc.
    • Humana, Inc.
    • Kaiser Permanente (Colorado, Northwest)
    • Vanderbilt/TennCare Bureau

Selection of Members: No Liver/Biliary Disease (Sub-Aim 1)

- **Inclusion criteria:**
  - 12 mo enrollment prior to diagnosis

- **Excluded:** Prior liver, biliary disease

- **Selected:**
  - 75 with toxic hepatitis diagnosis
  - 75 with ALF diagnosis

### Toxic Hepatitis

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>573.3</td>
<td>Toxic hepatitis</td>
</tr>
<tr>
<td>573.8</td>
<td>Other liver disorder (drug)</td>
</tr>
</tbody>
</table>

### Acute Liver Failure (ALF)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>570</td>
<td>Acute hepatic necrosis</td>
</tr>
<tr>
<td>572.2</td>
<td>Hepatic coma</td>
</tr>
<tr>
<td>572.4</td>
<td>Hepatorenal syndrome</td>
</tr>
<tr>
<td>572.8</td>
<td>Liver disease sequelae</td>
</tr>
<tr>
<td>V42.7</td>
<td>Liver transplant</td>
</tr>
</tbody>
</table>
Main Outcome: Severe Liver Injury

During hospitalization, observe either:

1) ALT or AST >3x ULN + total bilirubin >2x ULN
2) Total bilirubin >2x ULN + INR ≥1.5 (off anticoagulation)

ULNs via assay; Elevations need not be present on same day

Rationale:

- Def. 1: Liver injury interfering with bilirubin excretion
- Def. 2: May not be ↑ ALT/AST in advanced ALF

ULN = upper limit normal

Secondary Outcome: Acute Liver Failure (ALF)

• For members with ALF diagnoses, determined whether ALF occurred

• In absence of prior liver disease, observe both:
  1) INR \( \geq 1.5 \) (off anticoagulation therapy)
  2) Hepatic encephalopathy (altered mentation due to liver dysfunction)
    – Definition used by U.S. ALF Study Group*

Data Collection / Analysis

• Requested hospital records of selected members
• Redacted charts sent to Penn for abstraction
• Review by two hepatologists
  – Classified events: Definite; No; Unable to Determine
  – Disagreements: 3rd hepatologist broke ties
• Positive predictive value (PPV) of codes, combinations for definite severe liver injury, ALF
  – High PPV: identified outcomes are true diagnoses
Results: Confirmation of Events in Members with No Liver/Biliary Disease

149 Records requested

- 27 (18%) Did not provide records
- 17 (11%) Insufficient lab data to classify severe liver injury
- 105 (70%) Records sufficient to determine severe liver injury
- 57/75 (76%) Records sufficient to determine ALF
- 1/57 (2%) Confirmed ALF

122 (82%) Cases available for abstraction / adjudication

26 (17%) Confirmed liver injury
### Adjudicator Agreement

#### Arbitrator #1

<table>
<thead>
<tr>
<th></th>
<th>No SLI</th>
<th>SLI</th>
<th>Unable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No SLI</strong></td>
<td>69</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td><strong>SLI</strong></td>
<td>2</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td><strong>Unable</strong></td>
<td>1</td>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>

% agreement = 102/122 = 83.6%
### PPVs of Individual Diagnosis Codes for Confirmed Severe Liver Injury

<table>
<thead>
<tr>
<th>ICD-9-CM Code</th>
<th>No. with Code</th>
<th>No. with SLI</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SALI code</td>
<td>105</td>
<td>26</td>
<td>25%</td>
</tr>
<tr>
<td>573.3</td>
<td>26</td>
<td>11</td>
<td>42%</td>
</tr>
<tr>
<td>Hepatic necrosis</td>
<td>31</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>570</td>
<td>35</td>
<td>19</td>
<td>54%</td>
</tr>
<tr>
<td>572.2</td>
<td>23</td>
<td>3</td>
<td>13%</td>
</tr>
<tr>
<td>Liver disease sequelae</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>572.8</td>
<td>13</td>
<td>7</td>
<td>54%</td>
</tr>
<tr>
<td>V42.7</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>ICD-9-CM Combinations</td>
<td>No. with Codes</td>
<td>No. with SLI</td>
<td>PPV</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>Toxic hepatitis +</td>
<td>10</td>
<td>6</td>
<td>60%</td>
</tr>
<tr>
<td>Toxic hepatitis +</td>
<td>51</td>
<td>24</td>
<td>47%</td>
</tr>
<tr>
<td>Other specified liver disorder + Hepatic necrosis</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Hepatic necrosis + Liver disease sequelae</td>
<td>2</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>Liver disease sequelae</td>
<td>3</td>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>572.8 + liver biopsy code</td>
<td>7</td>
<td>7</td>
<td>100%</td>
</tr>
<tr>
<td>572.8 + liver biopsy code</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
</tbody>
</table>
## PPVs of Code(s) for Confirmed ALF

<table>
<thead>
<tr>
<th>ICD-9-CM Code or Combinations</th>
<th>No. with Code(s)</th>
<th>No. with ALF</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>570</td>
<td>33</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>572.2</td>
<td>22</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>572.4</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>572.8</td>
<td>11</td>
<td>1</td>
<td>9%</td>
</tr>
<tr>
<td>V42.7</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Any ALF code</td>
<td>57</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Any ALF code + liver biopsy</td>
<td>5</td>
<td>1</td>
<td>20%</td>
</tr>
<tr>
<td>Any ALF code + E-code</td>
<td>3</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
# Diseases Among 79 Members Adjudicated as No Severe Liver Injury

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis</th>
<th>Condition*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic necrosis (570)</td>
<td>DILI</td>
</tr>
<tr>
<td>Hepatic coma (572.2)</td>
<td>Alcoholic liver disease</td>
</tr>
<tr>
<td>Liver disease sequelae (572.8)</td>
<td>Alcoholic liver disease</td>
</tr>
<tr>
<td>Toxic hepatitis (573.3)</td>
<td>Cholelithiasis</td>
</tr>
<tr>
<td>Other liver disorder (drug) (573.8)</td>
<td>Hepatic cyst</td>
</tr>
</tbody>
</table>

* Not meeting severe liver injury criteria
Potential Study Limitations

- **Misclassification bias**
  - Standardized definitions for severe liver injury, ALF
  - Two adjudicators, third as tie-breaker

- **Small number of confirmed cases**

- **Negative predictive value not estimated**

- **Generalizability**
  - Commercially-insured; Tennessee Medicaid
Study Conclusions

• Individual ICD-9 codes had low PPV for liver injury, ALF
  – Lack of specificity of diagnosis codes
  – Complexity of diagnosis

• Select ICD-9 combinations had high PPV for liver injury:
  – Could evaluate comparative safety of drugs
  – Further validation prudent:
    • PPVs not determined using random samples
    • Sample sizes small
Electronic Data to Identify Liver Injury: Additional Methodologic Challenges

- Evaluate using lab data, labs + diagnoses
- Sensitivity of spontaneous reporting of DILI cases compared to case identification by electronic data
- Identification of appropriate controls
- Screen for liver injury in real time
- Predict adverse outcome at diagnosis of DILI
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