Prospective Analysis of Presenting Features of Neonatal Cholestasis – Limitations in Predictive Models of Biliary Atresia


Introduction

- Neonatal cholestasis is the presentation of a wide spectrum of serious disorders
- Timely and organized investigation is important
- In particular for biliary atresia

Research Sites

NIH National Institute of Diabetes and Digestive and Kidney Diseases

Clinical Sites

DCC NIH NIH Clinical Centers

NIH DCC Clinical Centers
Can one differentiate biliary atresia (BA) from nonBA at presentation? Informing clinical decision-making vis a vis further invasive testing

Hypothesis - Clinical parameters at presentation can be used to develop a model that precisely distinguishes BA from nonBA

Methods – Prospective Database of Infants with Cholestasis (PROBE)

PROBE – April 2004 to February 2014

Inclusion
- Age < 180 days
- DB or CB ≥ 2 mg/dL

Exclusion
- Acute liver failure, previous hepatobiliary surgery, sepsis, hypoxia, shock, malignancy, primary hemolytic disease, TPN-associated cholestasis, ECMO-associated cholestasis, BW < 1500g

NCT00061828
Methods – Definitions

- BA
  - Hepatopancreatoduodenostomy for BA, or
  - Exploration consistent with BA
- nonBA
  - Specific diagnosis associated with cholestasis
  - Idiopathic Neonatal Hepatitis (INH) or
  - Idiopathic Cholestasis (IC) required TB ≤ 1.0 at ≥ 120 days of age

Methods – Parameters

- PROBE Enrollment = presentation
- Clinical features
  - History - age at disease onset and at first evaluation, acholic stools, gender, race, ethnicity
  - Physical examination - weight, length, head circumference, MAC, facial features, liver BCM, spleen
  - Laboratory results - Total Bilirubin, Direct/Conjugated Bilirubin, ALT, AST, γ GT, Alk phos, alb, platelet count, cholesterol
  - Gallbladder sonography - present or absent (present includes “small”)

Methods – Analysis

- Primary analysis – BA vs nonBA
- Univariate
- Prediction Model Development
  - Logistic multivariate regression analysis (backward stepwise selection using alpha = 0.10 as the selection criteria)
  - Hierarchical classification and regression tree (CART)
  - AUC ROC
Results - Diagnoses

- BA, 401
- nonBA, 259

Results - Significant differences between BA and nonBA

<table>
<thead>
<tr>
<th></th>
<th>BA</th>
<th>nonBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>52.4%</td>
<td>36.7%</td>
</tr>
<tr>
<td>Disease onset (days)</td>
<td>12.8 ± 18.5</td>
<td>18.7 ± 22.1</td>
</tr>
<tr>
<td>WT z-score</td>
<td>-1.0 ± 1.0</td>
<td>-1.5 ± 1.2</td>
</tr>
<tr>
<td>Length z-score</td>
<td>-0.8 ± 1.5</td>
<td>-1.4 ± 1.5</td>
</tr>
<tr>
<td>Head circumference z-score</td>
<td>-1.1 ± 1.6</td>
<td>-1.4 ± 1.2</td>
</tr>
<tr>
<td>Acholic stools</td>
<td>82.4%</td>
<td>34.0%</td>
</tr>
<tr>
<td>Abnormal facial features</td>
<td>4.8%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>BA</th>
<th>nonBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver below costal margin (cm)</td>
<td>3.3 ± 1.6</td>
<td>2.5 ± 1.4</td>
</tr>
<tr>
<td>Palpable spleen</td>
<td>50.0%</td>
<td>40.4%</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.6 ± 0.5</td>
<td>3.5 ± 0.6</td>
</tr>
<tr>
<td>γGTP (IU/L)</td>
<td>712 ± 538</td>
<td>299 ± 380</td>
</tr>
<tr>
<td>Platelet count (x10⁹/L)</td>
<td>445 ± 180</td>
<td>420 ± 197</td>
</tr>
<tr>
<td>Absent gallbladder</td>
<td>39.9%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>
Results - Logistic Regression ROC

- Step 1 - acholic stools
- Step 2 - \(\gamma\)GTP
- Step 3 - GB absent
- Step 4 - Facial features
- Step 5 - Liver BCM
- Step 6 - Weight z-score
- Step 7 - Gender
- Step 8 - ALT
- Step 9 - disease onset

Results - Predicted Probability

* 224 infants predicted probability between 0.2 and 0.8
Results – Predicted Probability

* 224 infants predicted probability between 0.2 and 0.8

Results – CART Analysis

BA | nonBA
---|---
467 | 193

BA/ nonBA (467/193)

\( \text{GTP} \geq 203 \)
Results - CART Analysis

Missed BA
- Predicted probability < 0.2
- Predicted nonBA = 136
- True nonBA = 120,
- Missed BA = 16 (11.7%)
- CART – 16.5% erroneously categorized as nonBA

Overcalled BA
- Predicted probability > 0.8
- Predicted BA = 357
- True BA = 290,
- “Extra” investigations in 67 (18.8%)
- CART – 20.8% erroneously categorized as BA

Conclusions
- Significant differences exist in clinical features at presentation in BA vs nonBA
- Modeling not sufficiently precise to permit “highly informed” decisions based upon presenting clinical features
  - 10 – 20% chance to miss BA without further investigation
  - ~20% of infants undergo further investigations without BA
- Caution against making definitive decisions based upon these presenting clinical features in neonatal cholestasis