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

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Research Sites

Introduction

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

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

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Methods – Definitions

- BA
  - Hepatoportoenterostomy for BA, or
  - Exploration consistent with BA
- nonBA
  - Specific diagnosis associated with cholestasis
  - Idiopathic Neonatal Hepatitis (INH) or Idiopathic Cholestasis (IC) required TB $\leq$ 1.0 at $\geq$ 120 days of age

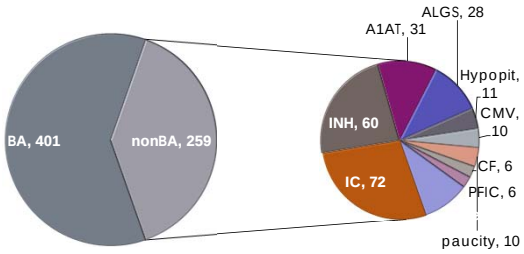
Methods – Parameters

- 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, γGTP, 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
  - Classification

Results - Diagnoses



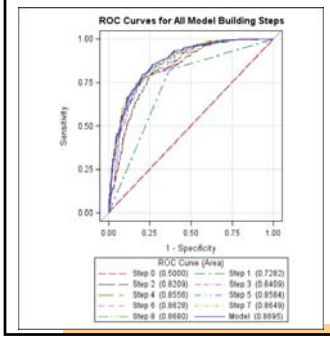
Results – Significant differences between BA and nonBA

	BA	nonBA
Female gender	52.4%	36.7%
Disease onset (days)	12.8 ± 18.5	18.7 ± 22.1
Wt z-score	-1.0 ± 1.0	-1.5 ± 1.2
Length z-score	-0.8 ± 1.5	-1.4 ± 1.5
Head circumference z-score	-1.1 ± 1.6	-1.4 ± 1.2
Acholic stools	82.4%	34.0%
Abnormal facial features	4.8%	18.8%

Results – Significant differences between BA and nonBA

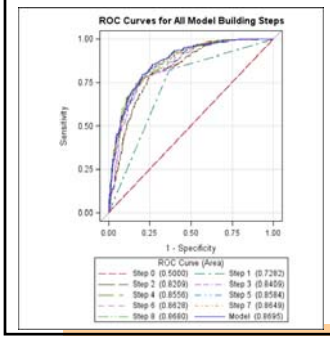
	BA	nonBA
Liver below costal margin (cm)	3.3 ± 1.6	2.5 ± 1.4
Palpable spleen	50.0%	40.4%
Albumin (g/dL)	3.6 ± 0.5	3.5 ± 0.6
γGTP (IU/L)	712 ± 538	299 ± 380
Platelet count ($x10^9$/L)	445 ± 180	420 ± 197
Absent gallbladder	39.9%	6.5%

Results – Logistic Regression ROC



- Step 1 – acholic stools
- Step 2 – γGTP
- 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 – Logistic Regression ROC



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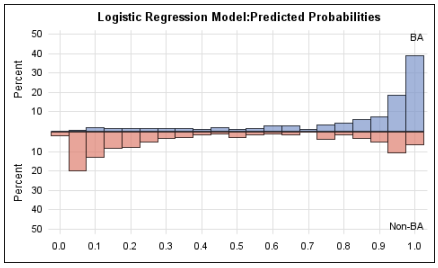
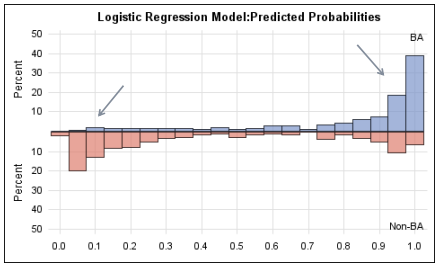
Results – Predicted Probability



* 224 infants predicted probability between 0.2 and 0.8

Results – Predicted Probability



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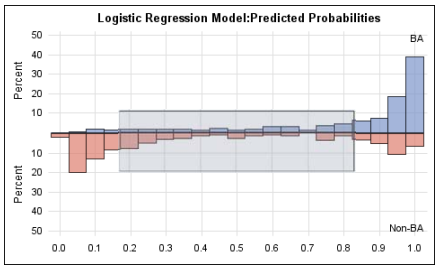

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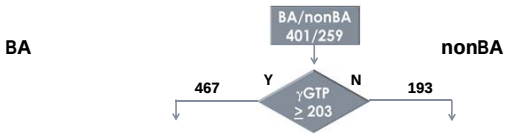
Results - CART Analysis



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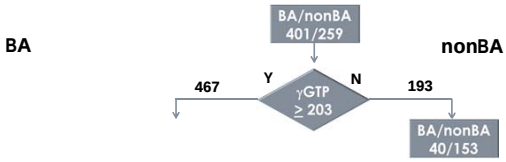

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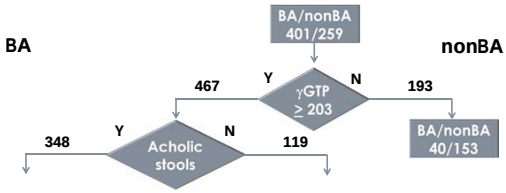

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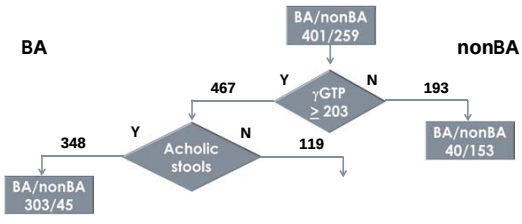

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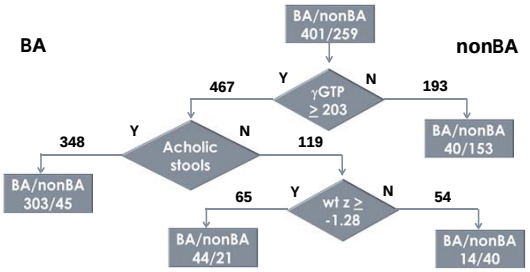

Results -

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