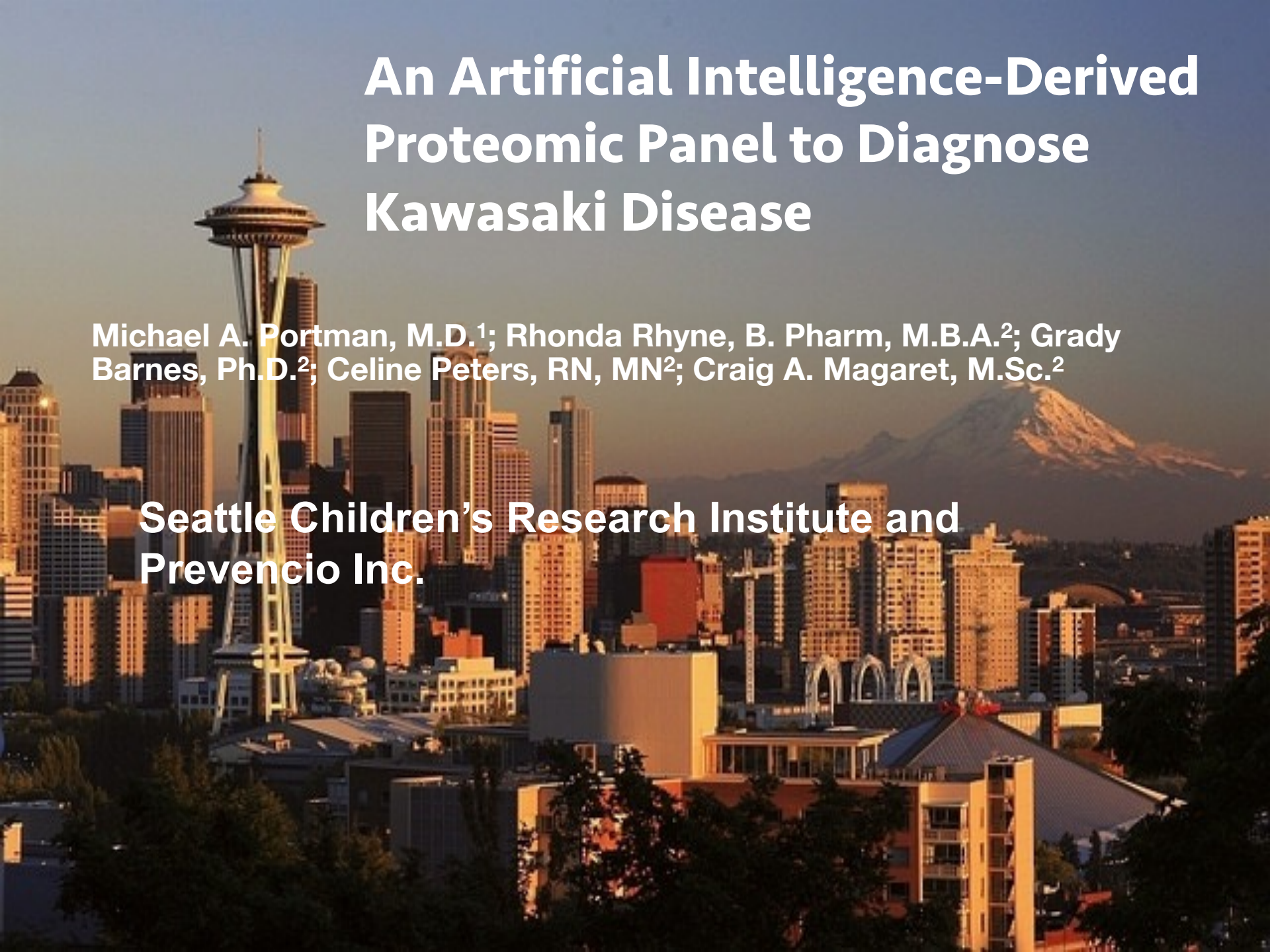

An Artificial Intelligence-Derived Proteomic Panel to Diagnose Kawasaki Disease

Michael A. Portman, M.D.[1]; Rhonda Rhyne, B. Pharm, M.B.A.[2]; Grady Barnes, Ph.D.[2]; Celine Peters, RN, MN[2]; Craig A. Magaret, M.Sc.[2]

Seattle Children's Research Institute and Prevencio Inc.

Disclosure

- M. A. Portman has No Conflicts to Disclose
- Rhonda Rhyne, Grady Barnes, Celine Peters, Craig A. Magaret are employees of Prevencio

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Background

- KD diagnosis based mainly on American Heart Association (AHA) or other professional society algorithms.
- KD clinical symptoms (2- 4) and laboratory values in addition to fever
- KD diagnosis often requires multiple ED or office visits due to < 4 KD criteria, even at tertiary care centers. (Lo, JPeds, 2021)

Background

- Early diagnosis is essential for treatment to avoid complications of KD.
- No specific or sensitive blood test or blood panel to rapidly confirm the KD diagnosis.
- KD diagnosis remains challenging for clinicians, particularly those rarely encountering KD.
- KD biomarker development has been restricted to individual protein levels or some sort of combination

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Objective

- Using proteomics and machine learning, a subset of Artificial Intelligence (AI), develop an accurate blood panel to diagnose KD
- Commercially viable panel for existing clinical laboratory platforms and analytes already FDA approved
- Optimized for 3 proteins or analytes to reduce complexity

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Artificial Intelligence

- Single proteins lack specificity and sensitivity
- Combining multiple proteins with individual cut offs also does not provide sufficient sensitivity and specificity for clinical applicability
- AI determines proper biomarkers and weighting for each protein or analyte

Study Design

We enrolled 150 children, presenting to the SCH ED with fever ≥ 38.1^{0}C. Samples were a mix of plasma and serum

- 100 blood samples from febrile children without KD (Control)
- 50 samples from children meeting AHA criteria for KD (prior to IVIG treatment)

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Study Cohort

All 50 KD patients were diagnosed within 5-10 days from fever onset

Temperature and age were available on each control subject with primary presenting symptom to ER

STUDY COHORT		
	Size	**Age in Months**
KD Cases	*n* = 50	45.9 (31.7)
Febrile Controls	*n* = 100	50.6 (37.1)
Total	*n* = 150	47.5 (33.6)

p = 0.45

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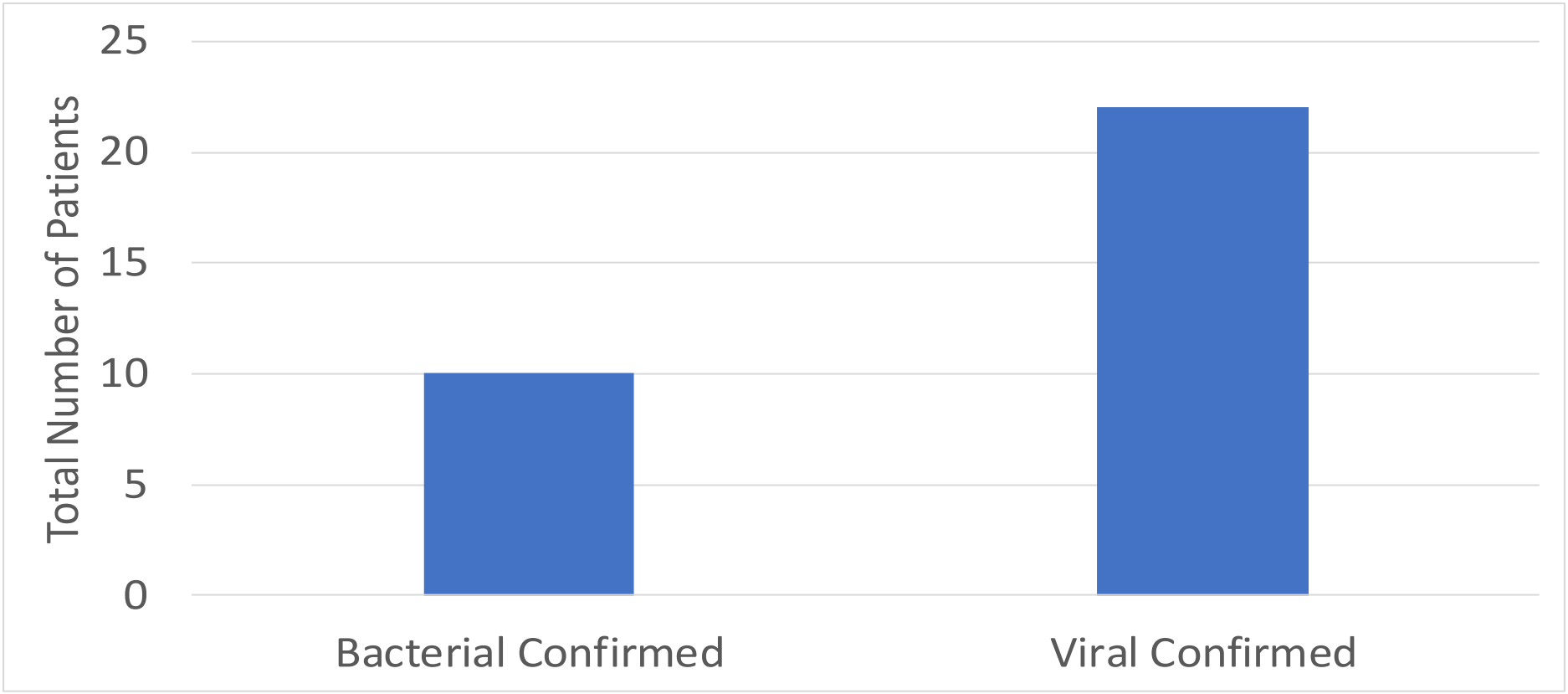
Control Patients Confirmed Infection



Blood Assays

- We assayed the blood samples for 42 analytes associated with KD on the Luminex 100/200 xMAP platform
- Enables broad exploration with small blood quantity

Blood Assays

11 analytes were included for the final analysis, based on commercial and clinical availability (FDA clearance)

- Apolipoprotein-a
- Beta 2 Microglobulin
- Immunoglobulin A
- Immunoglobulin M
- C Reactive Protein
- N-terminal prohormone of brain natriuretic peptide
- ST2

- **Thyroxine Binding Globulin**

Three additional assays on the Dimension Vista LOCI assay (Siemens)

- T Uptake (TU)
- Thyroid Stimulating Hormone (TSH)
- Free T4 (FT4)

Panel Discovery and Model Development

- The entire cohort of 150 patients was used for model training and in-sample validation
- The input features included
  - Patient age
  - The 11 assay results
- We used least-angle regression, a machine learning method, to select our final protein panel for KD diagnosis
- With this panel of features, a diagnostic model was trained using **Lasso,** another machine learning method

Final Panel with 3 Analytes

ASSAY RESULTS			
	Controls (*n* = 100)	**KD Cases (*n* = 50)**	***p*-value**
NT-proBNP (pg/mL)	116.5 (43.5, 248.8)	639.5 (198.5, 1722.5)	$p < 0.001$
CRP (ug/mL)	4.65 (2.7, 15.25)	124.0 (72.75, 209.25)	$p < 0.001$
TU (%)	31 (30, 33.75)	34 (32, 36)	$p < 0.001$

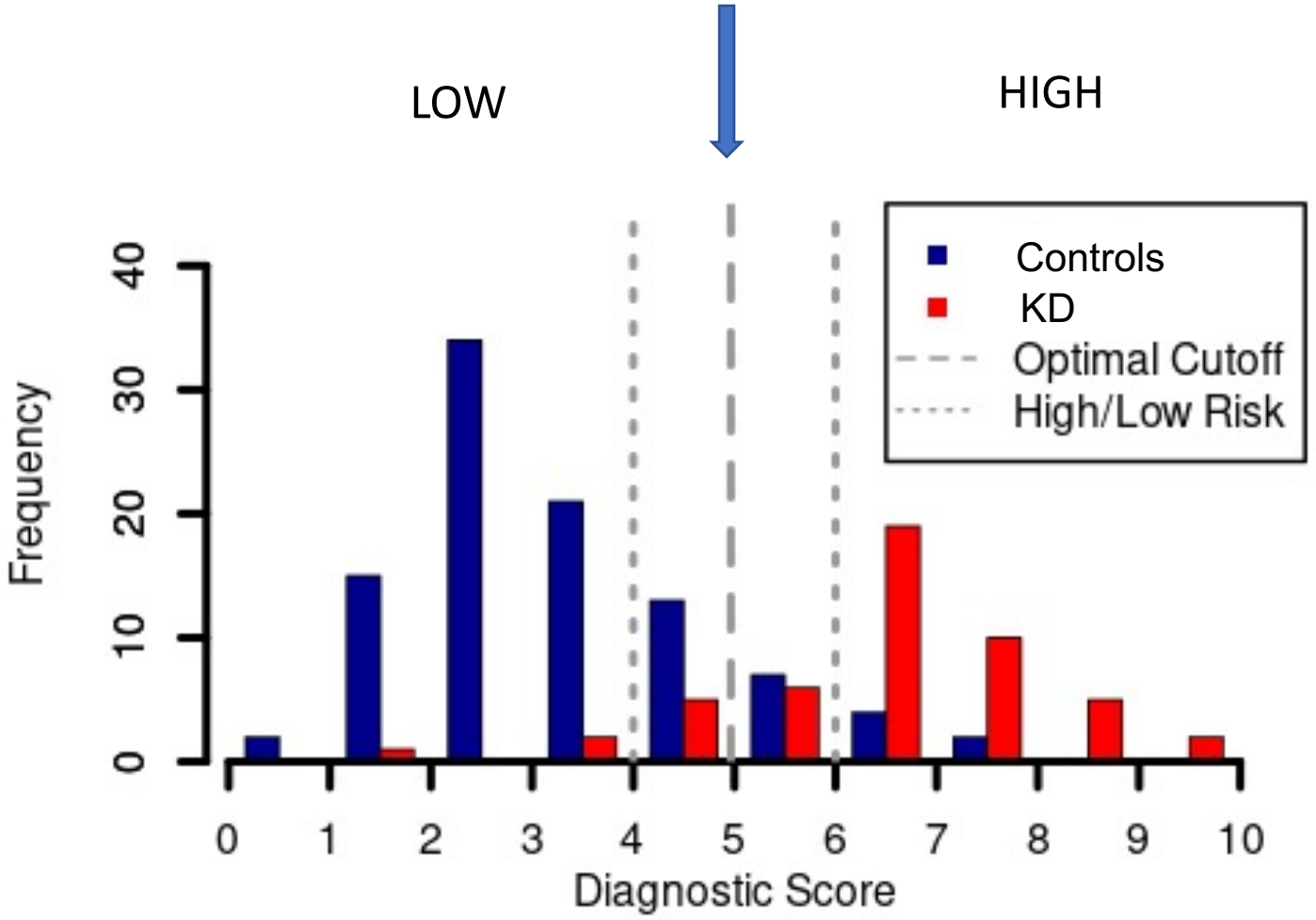
Model Evaluation

- Model performance was evaluated further with two different approaches:

  1. An optimal cutoff determined with Youden's index
     - (optimizes sensitivity and specificity), for positive or negative diagnoses resulting in binary classifier system

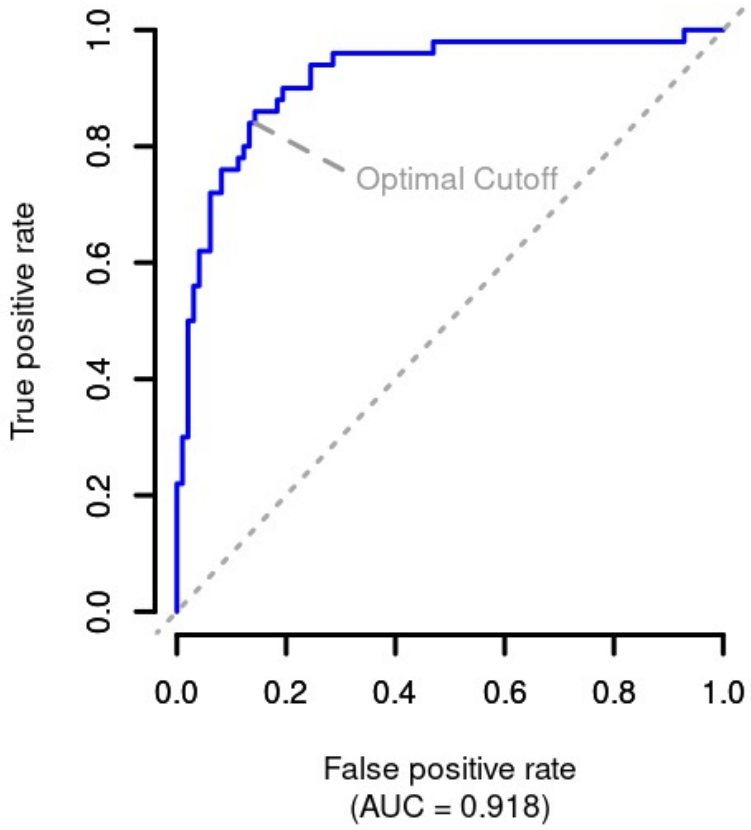
  2. Two cutoffs based on 10-point scale to create a three-level risk score
     - Low risk (0 -3), intermediate risk (4 -6), high risk(7-10)

AI - Model raw score rescaled to provide 10 point score



Model Performance

- **The model had a robust AUC of 0.92 (95% C.I.: 0.87, 0.96) for diagnosis of KD**



Model Performance Youden's Index

- At optimal cut-off (5):
  - 91 patients were diagnosed as negative
  - 57 as positive

MODEL PERFORMANCE
Optimal Cutoff
Sens. = 0.86 (0.76, 0.96)
Spec. = 0.86 (0.79, 0.93)
PPV = 0.75 (0.64, 0.87)
NPV = 0.92 (0.87, 0.98)

Model Performance

- Using our three-level risk score (1-3)
  - Low-risk patients (n = 75):
    - NPV = 0.96 (0.92, 1.0)
  - High-risk patients (n = 42):
    - PPV of 0.86 (0.75, 0.96)
  - 33 patients were diagnosed at intermediate risk

MODEL PERFORMANCE
Three-Level Risk Score
High Risk:
PPV = 0.86 (0.75, 0.96)
Low Risk:
NPV = 0.96 (0.92, 1.0)

Limitations

- Cohort was small and should be validated in a prospective study with a larger subject numbers
- the only clinical variable used for the control cohort was age (Waiver of Consent and HIPAA)

- Unable to assess impact of other clinical or demographic features, e.g., race or sex, which could enhance model

Conclusion

- CRP and NT-BNP individually were no surprise but do not provide clinical specificity for KD diagnosis
- AI and machine learning methods with addition of TU provide robust method of diagnosing KD
- All 3 assays can be run on same laboratory platform with results inputted to the AI model

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Conclusion

- Using a protein/analyte based approach and machine learning, we developed and internally validated a multiple blood assay panel with high accuracy for predicting the presence of KD.
- This panel can be performed on existing laboratory platforms and can provide a straightforward and rapid confirmation of KD diagnosis.
- In the ED or practitioner office, this KD panel could enhance and decrease time to diagnose, eliminate multiple patient visits and treat those patients positive for KD.