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A Division of HennepinHealthcare Research Institute

Exploring a New Framework for US Heart Allocation:

Development of an Evidence-Based Medical Urgency Score for Adult Heart Transplant Candidates

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BACKGROUND

- The US heart community has long advocated for a lab-based risk score to replace or supplement the current treatment-based 6-status allocation system for heart candidates:
  - Susceptible to gaming
  - Limited risk stratification

- In March 2024, the Organ Procurement and Transplantation Network (OPTN) Heart Transplantation Committee heard a proposal for a US candidate risk score (US-CRS) that was published in *JAMA* (Zhang et al, 2024).

- While the committee wanted to continue exploring the score, several members raised concerns about the underlying US-CRS model:
  - Impact of left ventricular assist devices (LVADs) on lab values
  - Real-world model performance?
  - Potential bias due to informative censoring at transplant

JAMA | Original Investigation

Development and Validation of a Risk Score Predicting Death Without Transplant in Adult Heart Transplant Candidates

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Supplemental content

IMPORTANCE The US heart allocation system prioritizes medically urgent candidates with a high risk of dying without transplant. The current therapy-based 6-status system is susceptible to manipulation and has limited rank ordering ability.

OBJECTIVE To develop and validate a candidate risk score that incorporates current clinical, laboratory, and hemodynamic data.

DESIGN, SETTING, AND PARTICIPANTS A registry-based observational study of adult heart transplant candidates (aged ≥18 years) from the US heart allocation system listed between January 1, 2019, and December 31, 2022, split by center into training (70%) and test (30%) datasets. Adult candidates were listed between January 1, 2019, and December 31, 2022.

MAIN OUTCOMES AND MEASURES A US candidate risk score (US-CRS) model was developed by adding a predefined set of predictors to the current French Candidate Risk Score (French-CRS) model. Sensitivity analyses were performed, which included intra-aortic balloon pumps (IABP) and percutaneous ventricular assist devices (VAD) in the definition of short-term mechanical circulatory support (MCS) for the US-CRS. Performance of the US-CRS model, French-CRS model, and 6-status model in the test dataset was evaluated by time-dependent area under the receiver operating characteristic curve (AUC) for death without transplant within 6 weeks and overall survival concordance (c-index) with integrated AUC.

RESULTS A total of 16 905 adult heart transplant candidates were listed (mean [SD] age, 53 [13] years; 73% male; 58% White); 796 patients (4.7%) died without a transplant. The final US-CRS contained time-varying short-term MCS (ventricular assist-extracorporeal membrane oxygenation or temporary surgical VAD), the log of bilirubin, estimated glomerular filtration rate, the log of B-type natriuretic peptide, albumin, sodium, and durable left ventricular assist device. In the test dataset, the AUC for death within 6 weeks of listing for the US-CRS model was 0.79 (95% CI, 0.75-0.83), for the French-CRS model was 0.72 (95% CI, 0.67-0.76), and 6-status model was 0.68 (95% CI, 0.62-0.73). Overall c-index for the US-CRS model was 0.76 (95% CI, 0.73-0.80), for the French-CRS model was 0.69 (95% CI, 0.65-0.73), and 6-status model was 0.67 (95% CI, 0.63-0.71). Classifying IABP and percutaneous VAD as short-term

PRIMARY AIM

The aim of this study is to resolve the OPTN committee's concerns in an updated cohort and propose a new "US-CRS 2.0" risk score for allocation of donor hearts to adult heart candidates.

METHODS

US-Candidate Risk Score 1.0 (Zhang et al, 2024)

- Scientific Registry of Transplant Recipients (SRTR) data
- Training set: New listings from Jan. 1, 2019 – Dec. 31, 2022
- Outcome: Death within 6 weeks
- Landmark discrete-time survival model for 6-week hazard
- 7 patient variables:
    - 5 lab values (linear effects): albumin, bilirubin, estimated glomerular filtration rate (eGFR), B-type natriuretic peptide (BNP), sodium
    - Short-term mechanical circulatory support (eg, extracorporeal membrane oxygenation [ECMO])
    - Durable LVAD
- No adjustment for informative censoring
- Standard assessment of model performance
    - Held-out data from 2019-2022, split by center

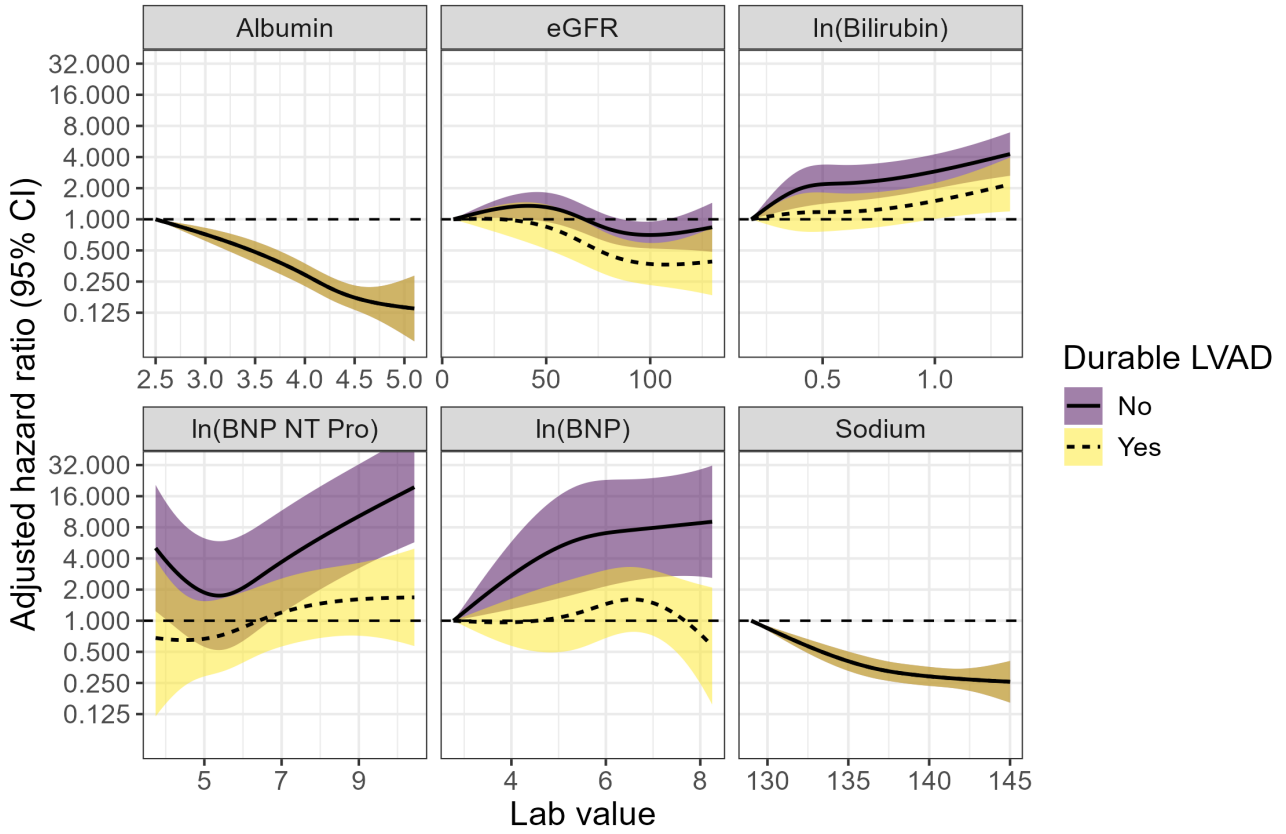
US-Candidate Risk Score 2.0 (current study)

- SRTR data
- Training set: Prevalent cohort of all adult heart candidates waiting from Jan. 1, 2019 – Dec. 31, 2022
- Outcome: Death or removal for deteriorated condition within 6 weeks
- Landmark discrete-time survival model for 1-week hazard
- Patient variables: US-CRS 1.0 covariates + nonlinear effects + hemodynamic values + interactions of lab values with durable LVAD + time on LVAD
- Inverse probability of censoring weights
    - Sicker candidates receive transplant
- Real-world model performance:
    - Assess model discrimination among patients competing for the same donor hearts, in 6-week cohorts in 2023

MODEL RESULTS

Model training data:

- N=18,877
- Waitlist mortalities: 1,688
  - 765 deaths
  - 923 removals for deteriorated condition
- Patient variables selected by Akaike Information Criterion:
- All US-CRS 1.0 variables
- Nonlinear effects
- Interactions of durable LVAD use with log bilirubin, eGFR, and log BNP
- Two hemodynamic measures:
  - Aortic pulsatility index
  - Pulmonary artery pulsatility index
- Years on LVAD



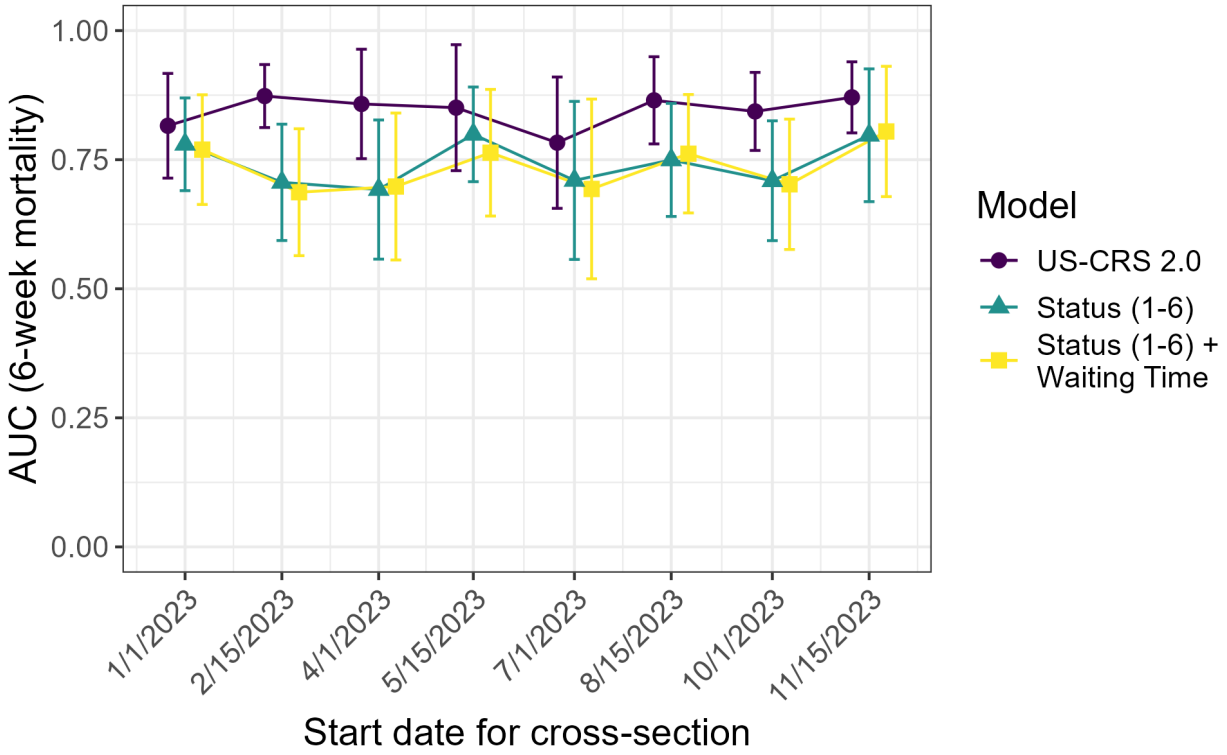
REAL-WORLD MODEL PERFORMANCE: DISCRIMINATION

Time-dependent area under the receiver operating characteristic curve (AUC)

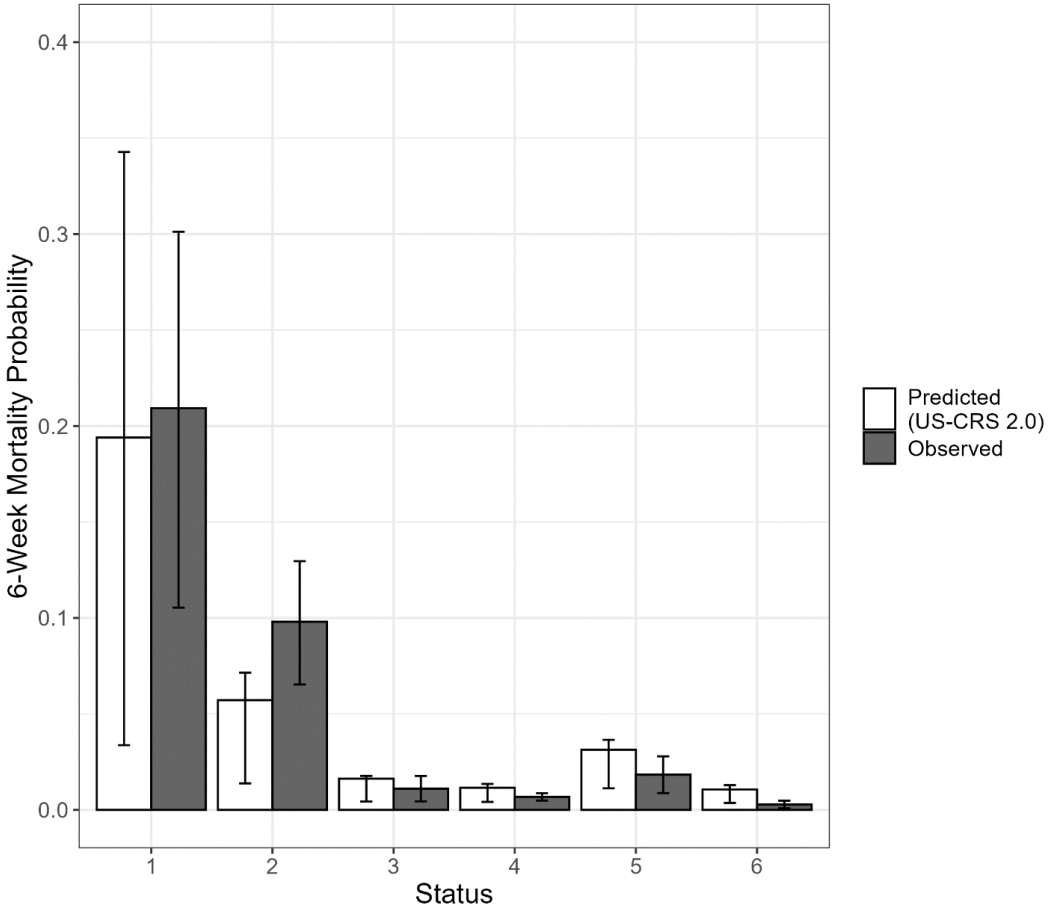
Higher values → better ability to discriminate risk of 6-week mortality

6-week cross-sections of test set:

- Includes all candidates active and still waiting at start of cross-section
- Candidates who are “competing” with each other for donor hearts



MODEL PERFORMANCE: CALIBRATION BY STATUS



Calibration: Do predicted probabilities correspond to observed mortality in 2023 test data?

By medical urgency status in current system

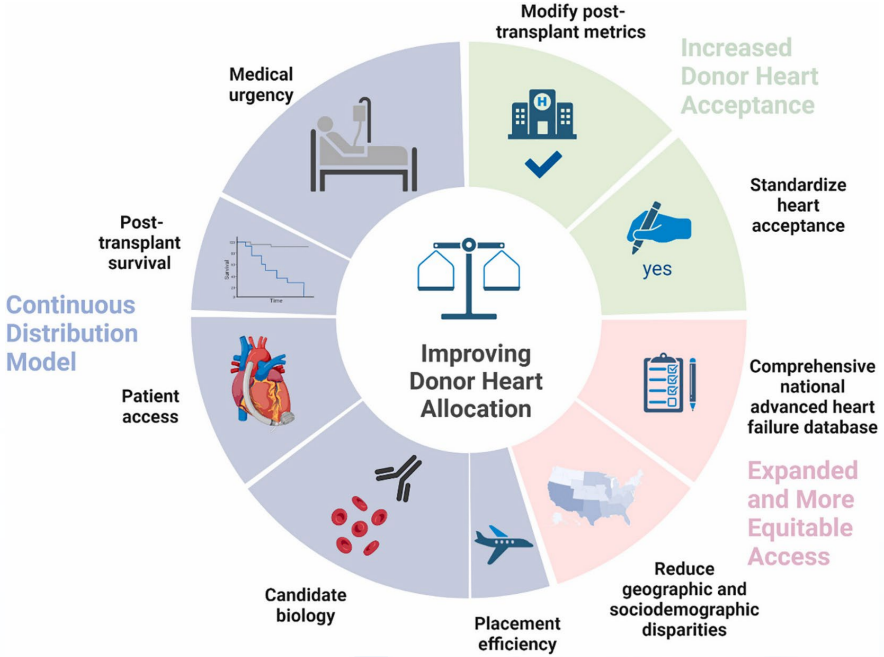
- Status 1: Highest risk, highest priority

- Analysis results:
- US-CRS 2.0 somewhat underestimates risk for Status 2, overestimates risk for Status 6 patients

CONCLUSION

US-CRS 2.0 expands on US-CRS 1.0 with:

- Nonlinear effects
- Effect modification by LVAD use
- Hemodynamic variables
- Time on LVAD
- Adjustment for informative censoring



Khush et al, 2023

- Next steps:
- Develop a method of assigning points to candidates with higher predicted mortality
- Continue collaborating with OPTN Heart Committee, collecting community feedback

Questions?

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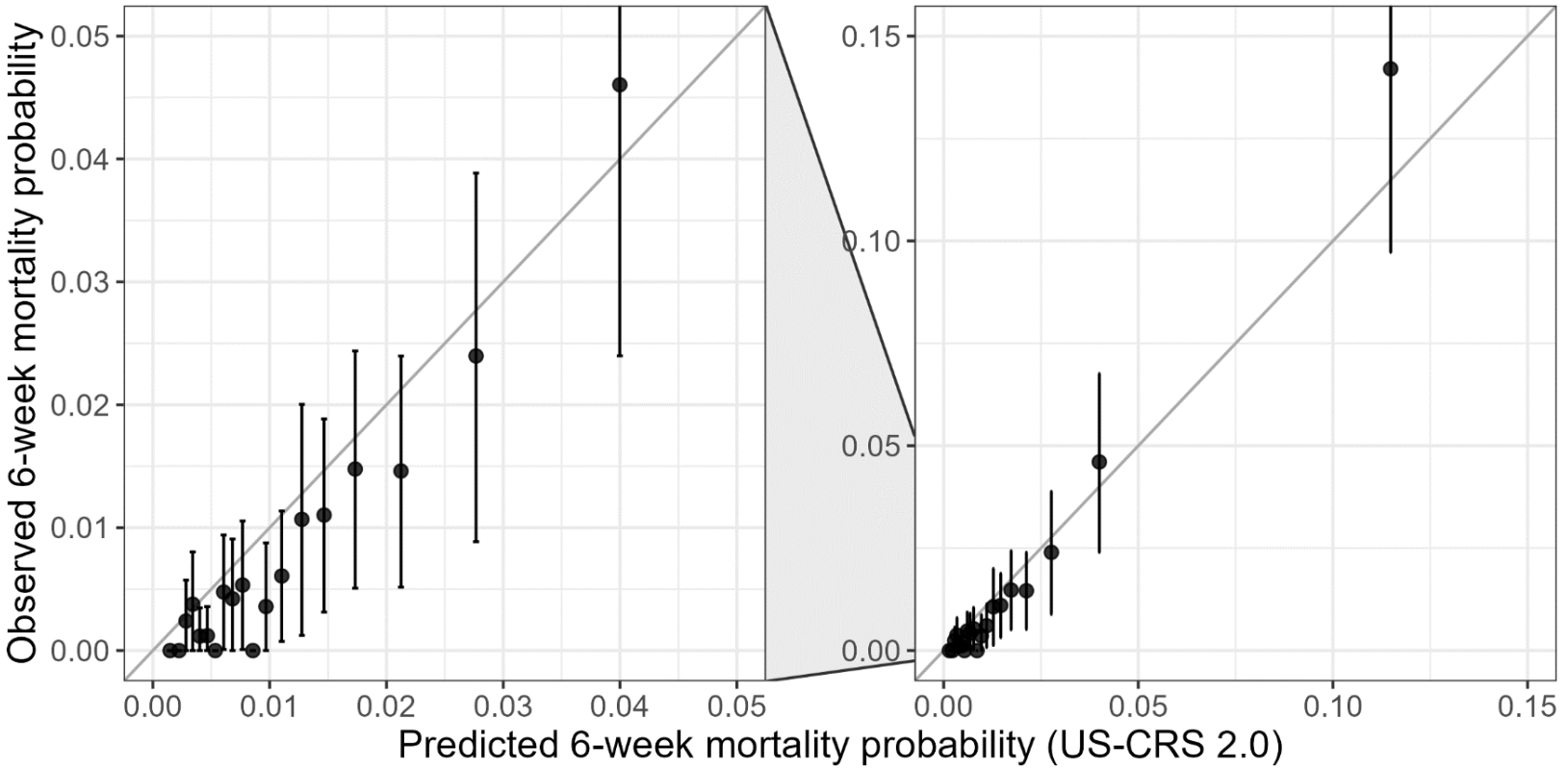
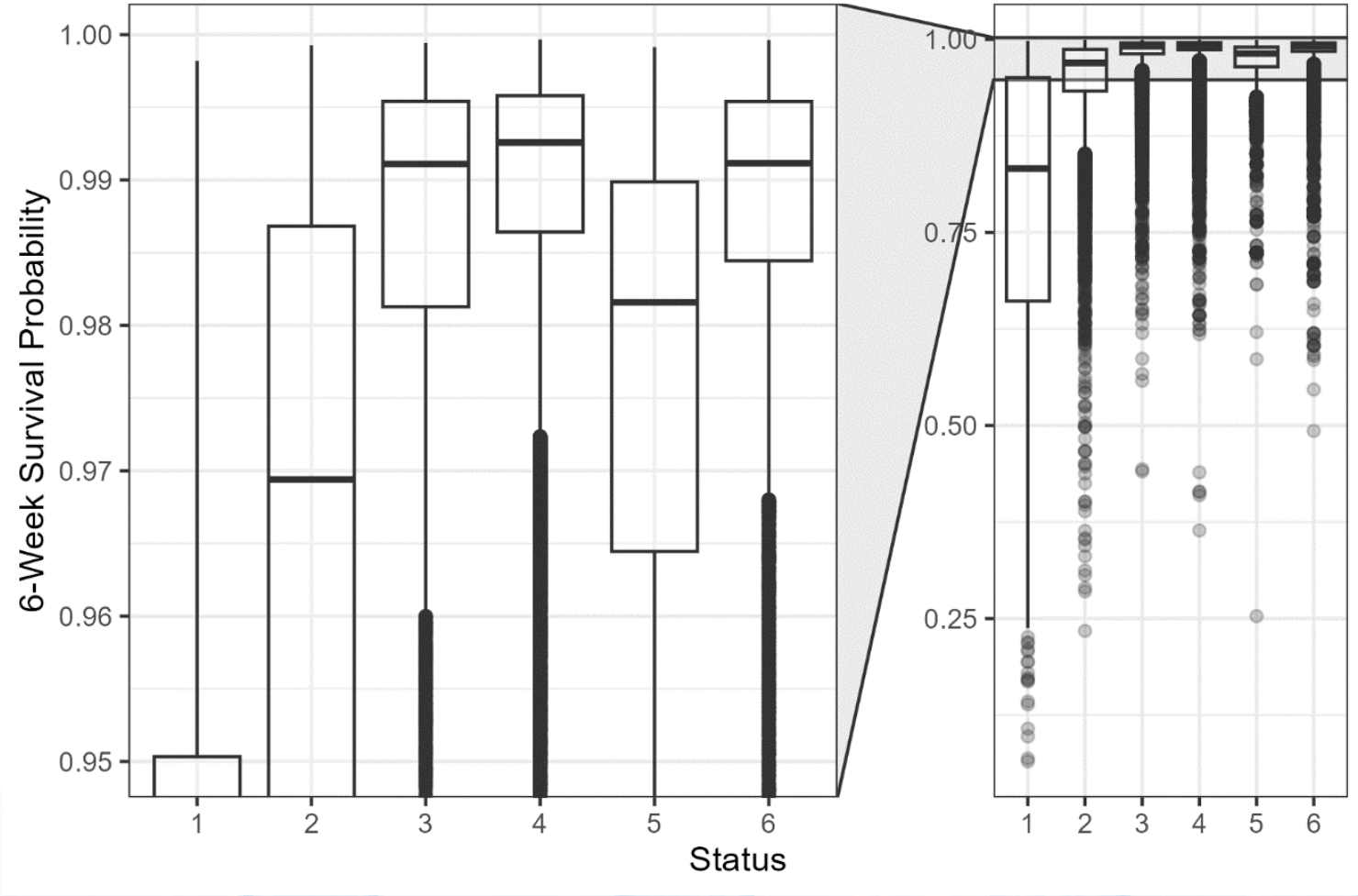
SUPPLEMENTAL SLIDES

MODEL CALIBRATION OF US-CRS 2.0



PREDICTED PROBABILITIES BY STATUS



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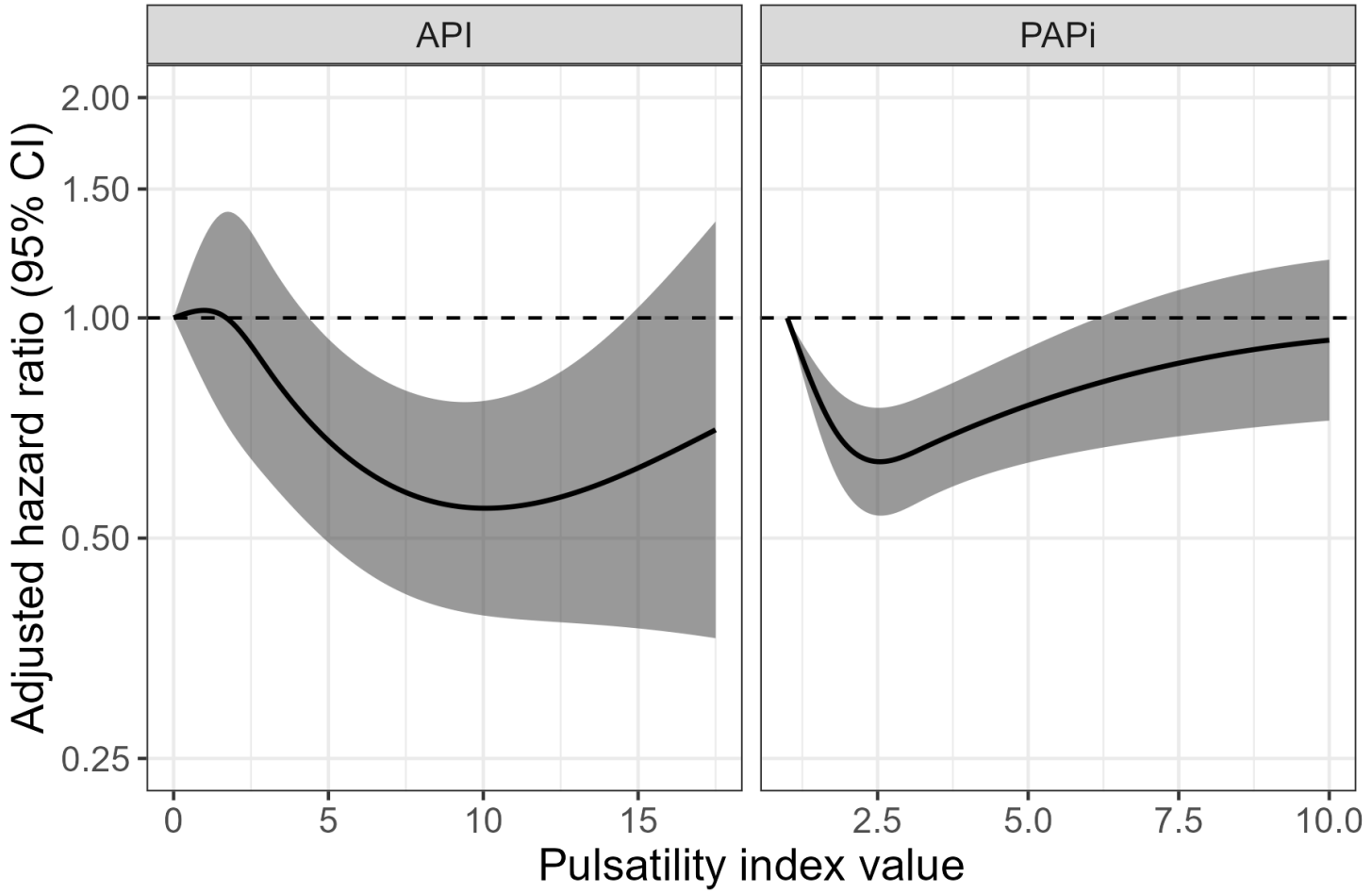
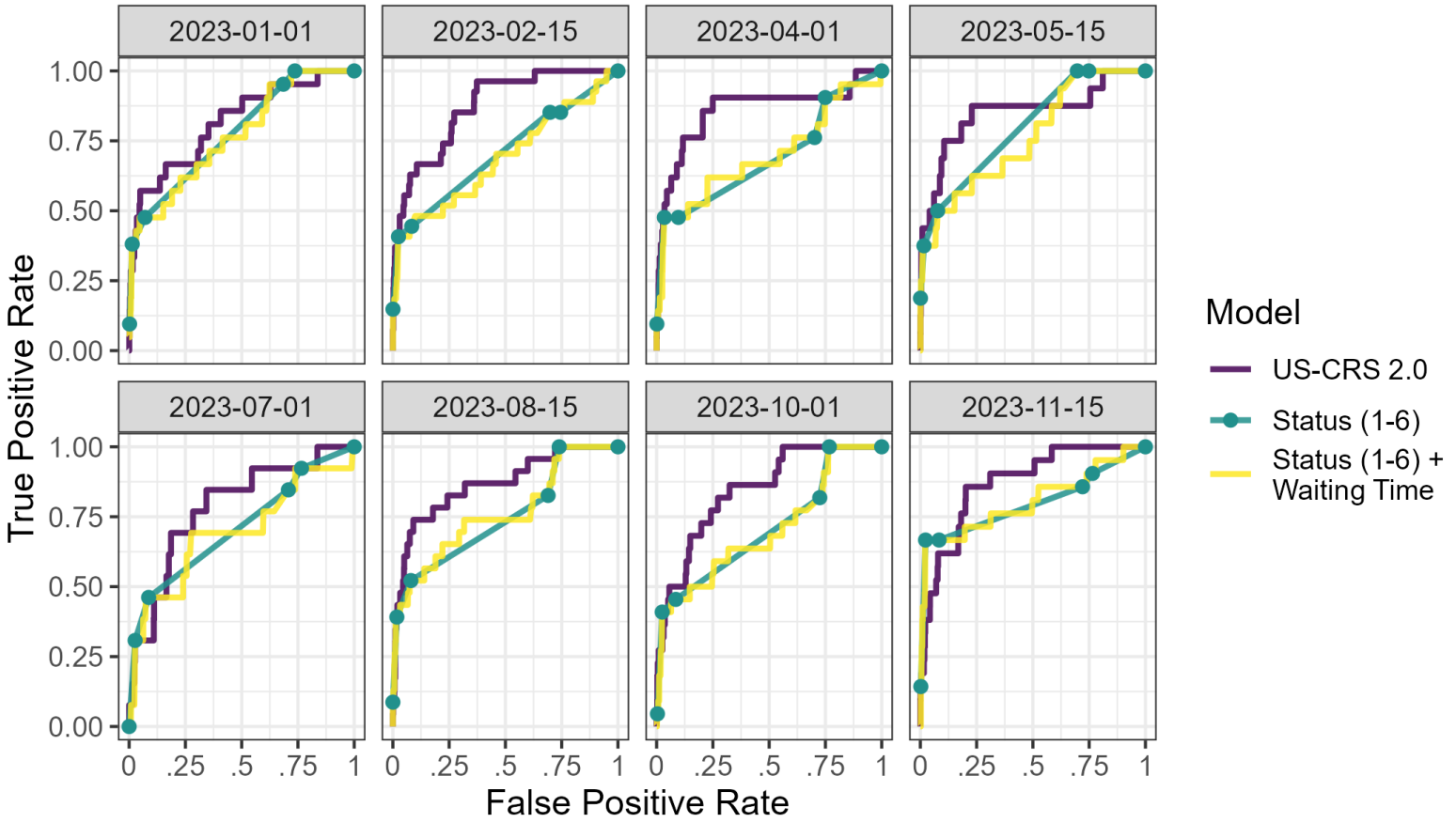

API
PAPi
Adjusted hazard ratio (95% CI)
2.00
1.50
1.00
0.50
0.25
0
5
10
15
2.5
5.0
7.5
10.0
Pulsatility index value


2023-01-01
2023-02-15
2023-04-01
2023-05-15
2023-07-01
2023-08-15
2023-10-01
2023-11-15
True Positive Rate
False Positive Rate
0.00
0.25
0.50
0.75
1.00
0
.25
.5
.75
1
Model
US-CRS 2.0
Status (1-6)
Status (1-6) + Waiting Time

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