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Lecture 3:

Predicting Septic Shock and Its Progression

Sepsis & Septic Shock

Sepsis:

A system-wide severe infection leading to reduced blood pressure , organ perfusion, and possibly organ failure and death

Mortality:

US ~ 20-50%

Impact:

30-50% of all hospital deaths

Most expensive disease to treat

Leading cause of hospital readmission

*Liu et al (2014) *JAMA* 312(1):90-92

The “Natural Time Course” of Sepsis & Septic Shock

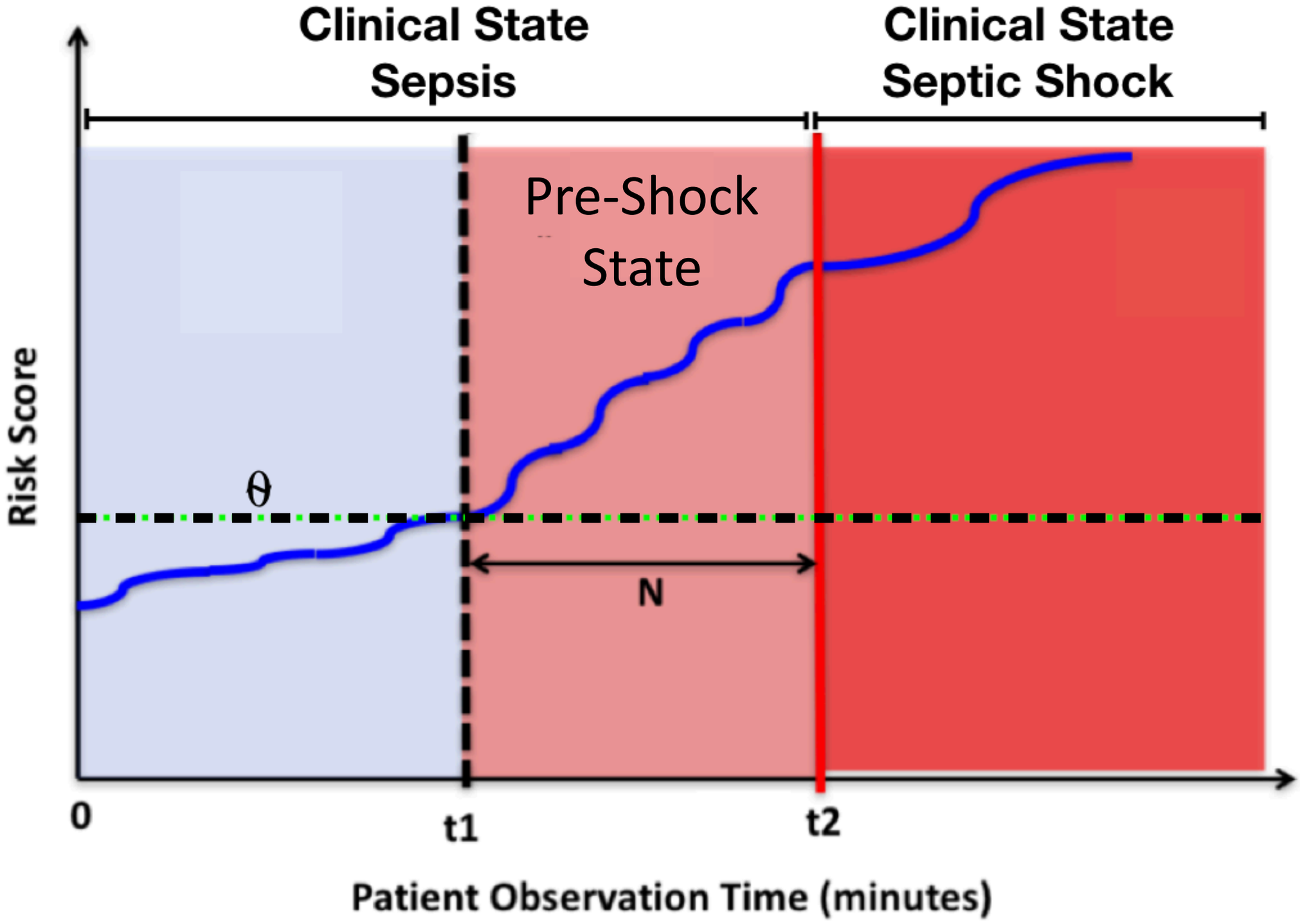
Mortality in septic shock increases ~ 8% for every hour of delayed treatment*

Early treatment improves outcomes

Challenge:
Provide data-driven, objective, reliable early warnings in sepsis patients of impending septic shock before this clinical transition occurs to enable early therapy

*Kumar et al (2006) *Crit Care Med* 34:1589-96

The Key Hypothesis



*Liu et al (2019) *Nat. Sci. Repts. 9: 6145*

Approach

- MIMIC-II ***adult*** ICU numeric (minute-to-minute) & EHR data
- Apply Sepsis-III* Consensus definitions of sepsis and septic shock to determine clinical states of every patient over time (ground-truth)
- Use Generalized Linear Modeling (GLM) to calculate a risk score from patient features
- With this risk score, use training data to build a classifier to predict impending septic shock in patients with sepsis
- Evaluate classifier performance on test data

*Singer et al (2016) *JAMA* 315(8): 801-810

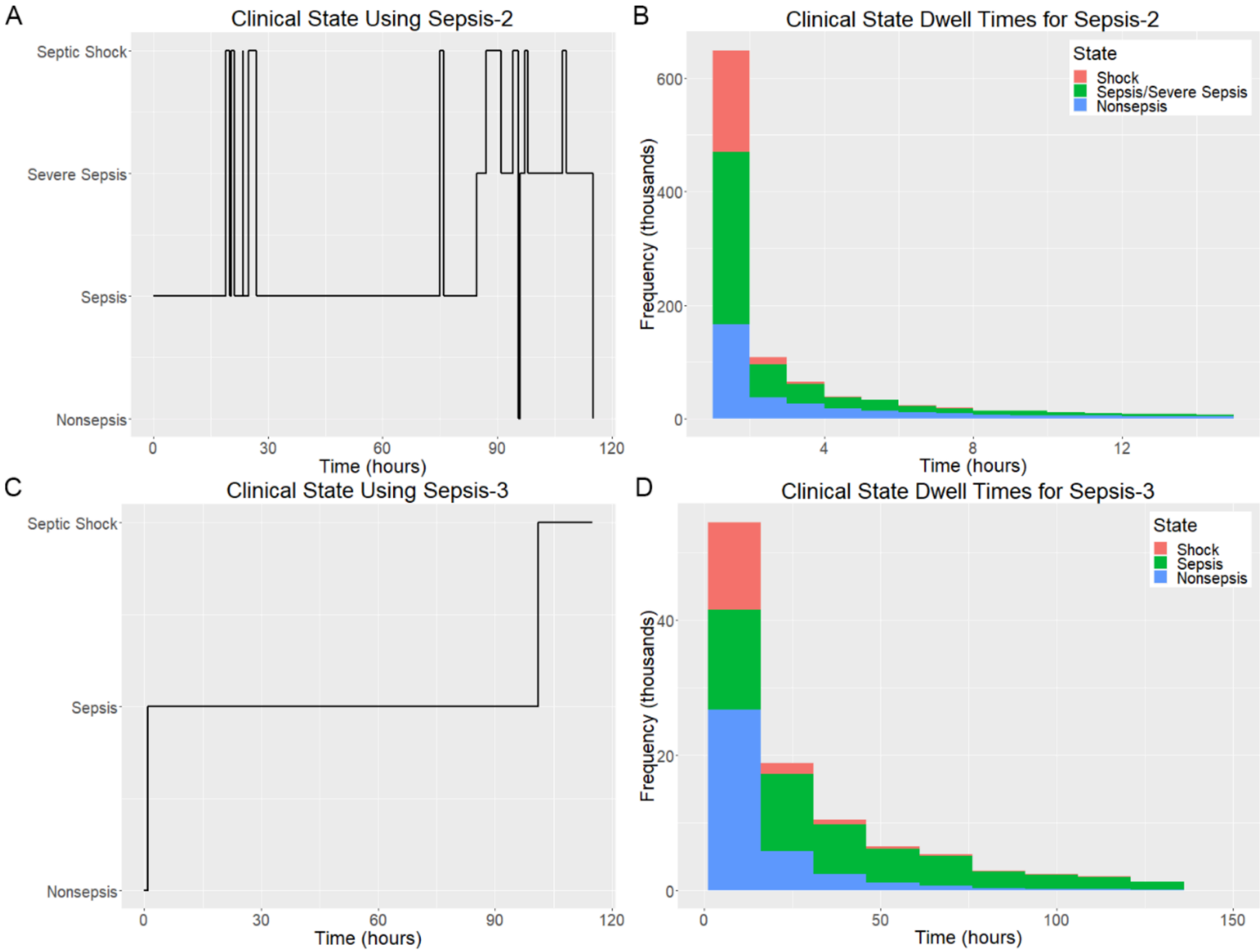
Sepsis-3 Definitions*

- **Sepsis**
  - suspected infection AND
  - Two or more of the following; AND
    - Respiratory rate ≥ 22/min OR
    - systolic blood pressure ≤ 100 mm-Hg OR
    - Glasgow coma score ≤ 13
    - sequential organ failure assessment score ≥ 2

- **Septic shock**
  - sepsis AND
  - despite adequate fluids, vasopressors needed to maintain MAP ≥ 65 mm-Hg AND
  - serum lactate > 2 mM/L

*Singer et al (2016) *JAMA* 315(8): 801-810

Sepsis-2 Clinical State Labels are Temoporally Unstable



- mean number label changes per patient
  - Sepsis-2 16
  - Sepsis-3 1

Features, Risk Model, Decisions

Features :

- Lactate, Glasgow coma score (GCS), sequential organ failure assessment (SOFA) scores, FiO_2
- heart rate, PaO2, respiratory rate

Training Set $\{(\underline{X}_i, Y_i = y_i), i = 1,\ldots,N\}$:

- $y_i = 0$ for feature vectors from patients with sepsis and no shock
- $y_i = 1$ for feature vectors from one-hour window preceding shock
- N class labels are independent Bernoulli observations

$$P(Y_i = y_i) = p_i^{y_i}\left(1-p_i\right)^{1-y_i} \qquad y_i \in \{0,1\}$$

Features, Risk Model, Decisions

GLM Time-Evolving Risk Score p(X(t),β):

$$p\left(\underline{X}(t),\underline{\beta}\right)=\frac{e^{\underline{X}(t)^T\underline{\beta}}}{1+e^{\underline{X}(t)^T\underline{\beta}}}$$

$$L(\underline{\beta})=\prod_{i=1}^{N}p(\underline{X}_i,\underline{\beta})^{y_i}\left(1-p(\underline{X}_i,\underline{\beta})\right)^{1-y_i}-\lambda\sum_{i=1}^{M}\left|\beta_i\right|$$

Likelihood Function L1-penalty

MLE of β

Decisions:

$p(\underline{X}(t),\underline{\beta})>\theta$ predict pending shock

Advantages of This Approach

Interpretable Decision Rule !

	Variable	Coefficient	SE
Numeric	Intercept	-2.974330922	0.009551231
	HR	0.292503877	0.006985994
	SBP	-0.252831939	0.006893423
	PaO_2	0.429659115	0.00438058
EHR	GCS	-0.634782631	0.005989372
	Lactate	0.733257393	0.00661599
	BUN	0.225824586	0.006995195
	WBC	0.285014711	0.005484431
	SOFA (Respiratory)	0.231603804	0.005592707
	SOFA (Coagulatory)	0.284541533	0.006787376
	SOFA (CV)	0.614226176	0.005742869

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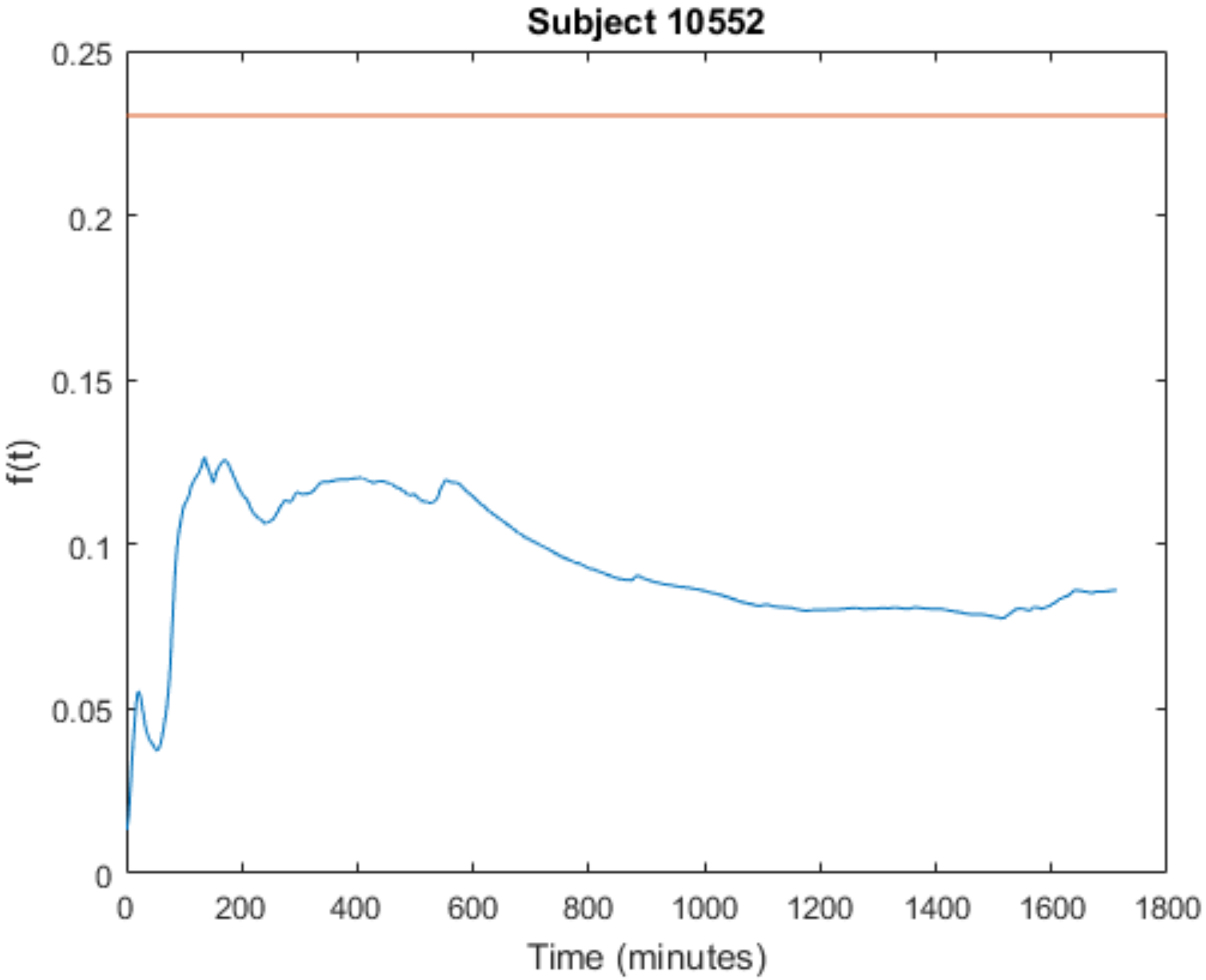
Some Examples

Patient never transitions to shock



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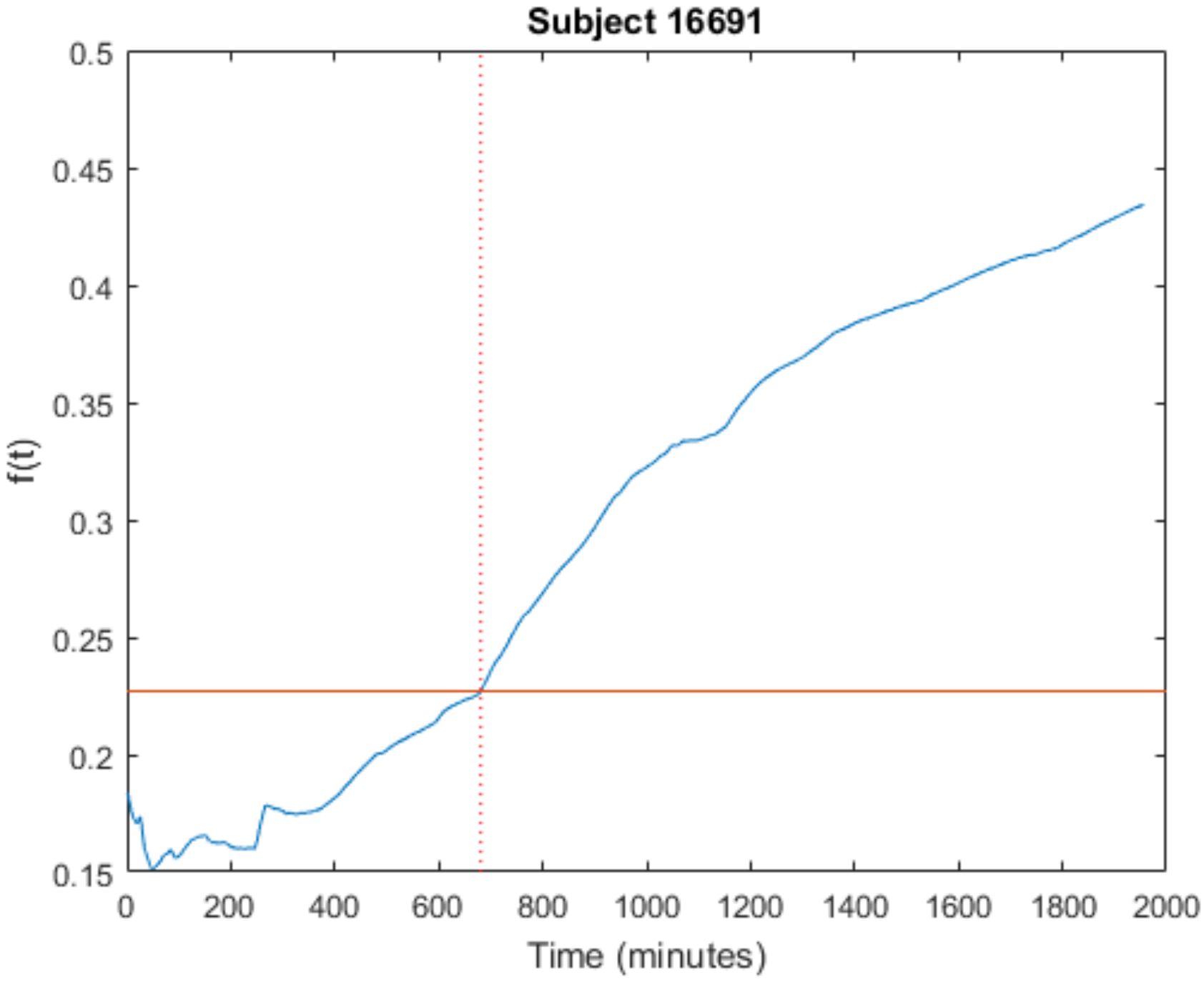
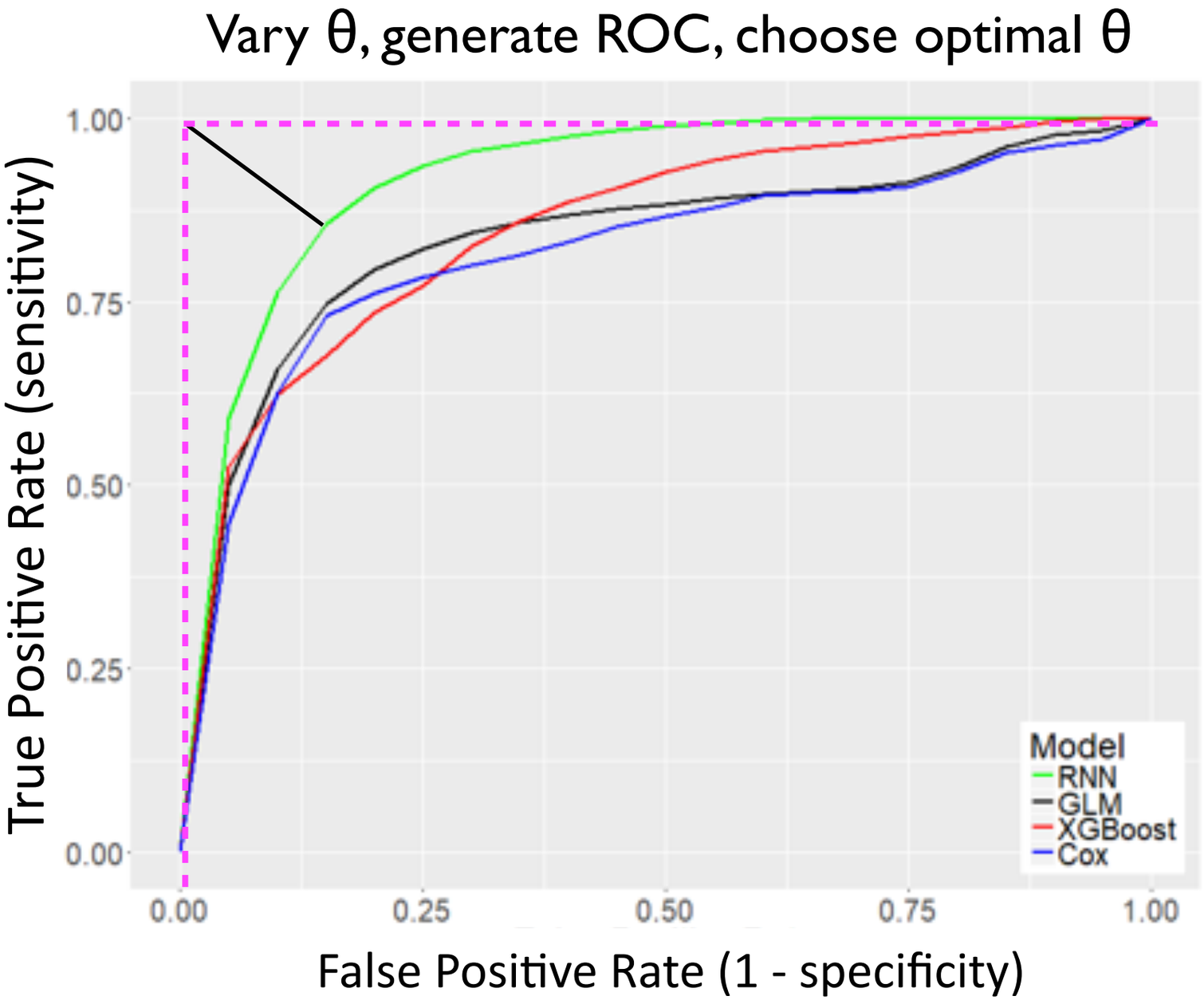
Some Examples

Shock detected at 681 min, shock onset 2076 min, 23.25 hour early warning time



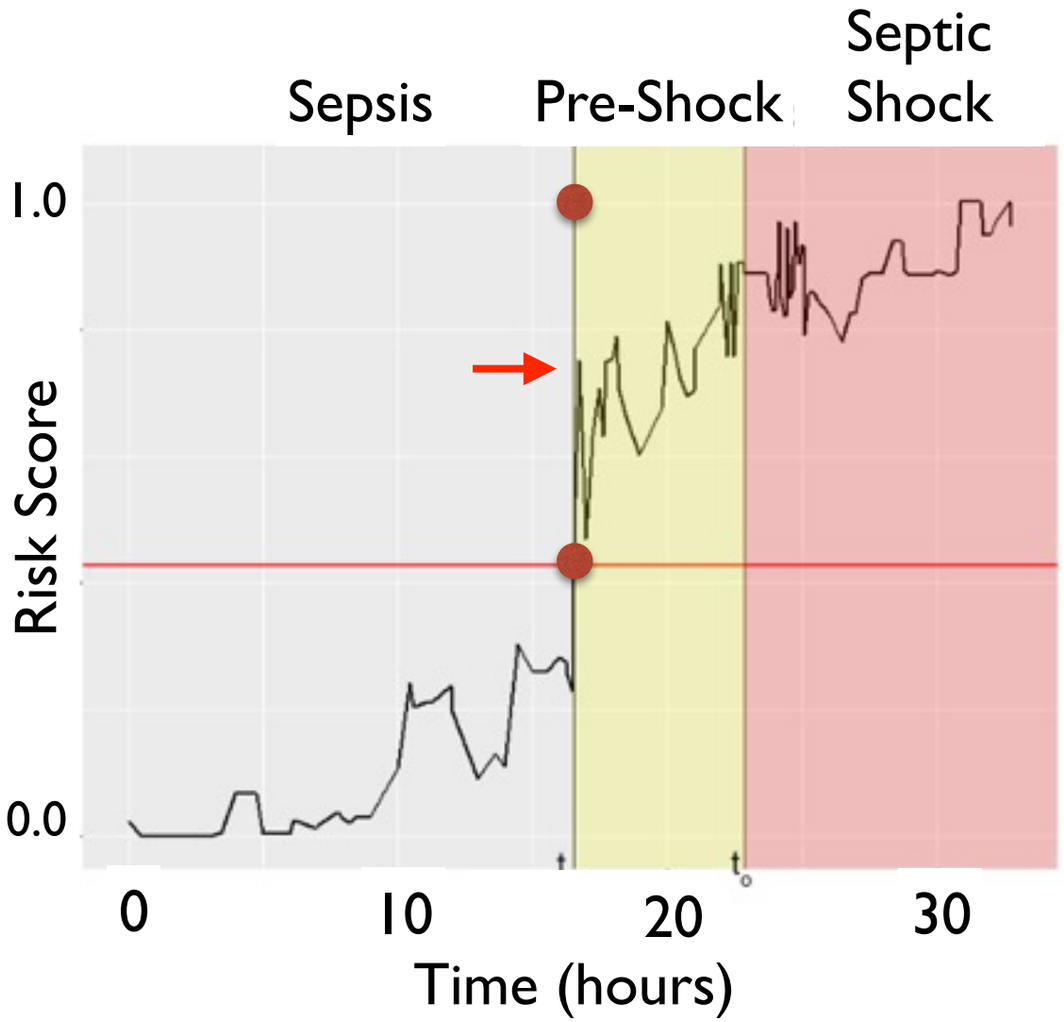
Performance

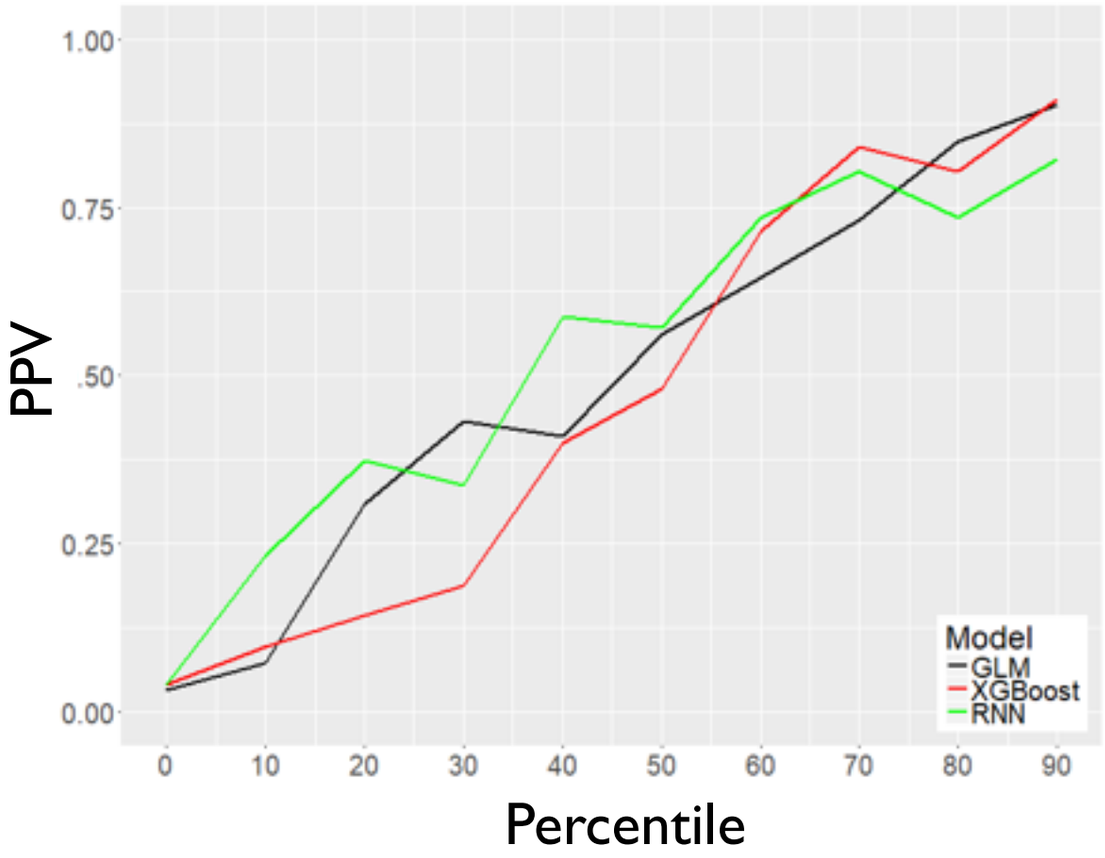


- sensitivity 88%, specificity 84%, AUC .93, *Average PPV .52*
- Median early warning time 7 hours

*Liu et al (2019) *Nat. Sci. Repts. 9: 6145*

Patient-Specific Positive Predictive Value (PPV)





Conclusions:

- Risk score immediately after threshold-crossing determines PPV
- patient-specific PPV aids decision-making by physicians
- *note the rapid change in risk score during entry into the pre-shock state*

*Liu et al (2019) *Nat. Sci. Repts. 9: 6145*

OK, This is Where We Are Right Now

- Sepsis-3 clinical state labels are temporally stable, Sepsis-2 are not
- Fairly reliable early warning of impending septic shock (sensitivity 88%, specificity 84%, AUC .93)
- Median 7 hour early warning time
- patient-specific PPV can be assigned to warning

How Does Patient Risk Evolve After Detection?

- Do temporal profiles of risk score organize into distinctive patterns (clusters) ?
- If yes, how do patient attributes differ between clusters?

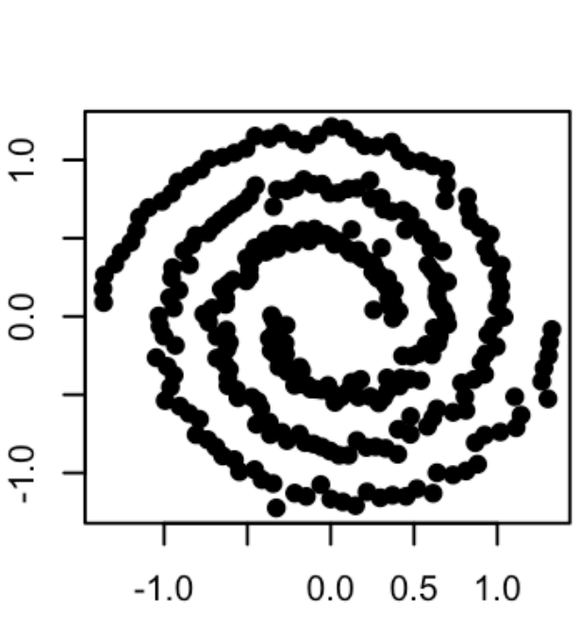
Align time-evolving risk scores at threshold crossing time
Apply spectral clustering to discover temporal classes

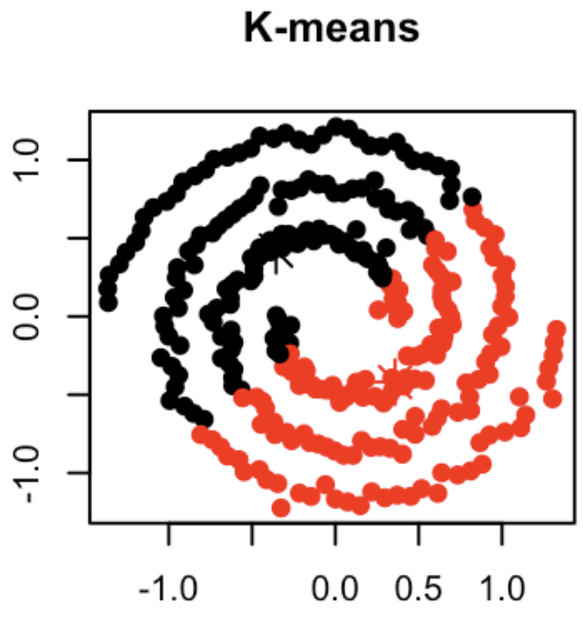
Spectral clustering: Overview

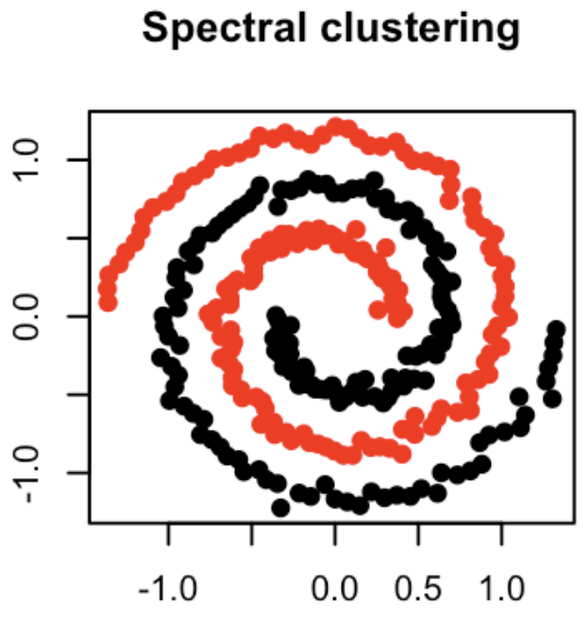
- Spectral clustering is a non-linear clustering algorithm
- It chooses clusters which minimize distance between points in the same cluster, while maximizing distances between points in different clusters

Linear vs non-linear clustering algorithms

- K-means is a commonly used linear clustering algorithm, meaning that boundaries between clusters are linear
- The tradeoff is in computation time: Non-linear clustering methods are more computationally intensive







How does spectral clustering work?

- Data are represented in a new space defined by the eigenvectors of the graph Laplacian matrix L:

$$L = DM - A$$

- DM is “Degree Matrix”, A is “Adjacency Matrix”

What Is L = DM – A ?

Assume N time-series $\hat{p}_i(t)$ {i=1,…,N}, {t= t_1,…, t_M}

Define a distance matrix D with elements d_{ij} that are distances between time-series

$$d_{ij} = \sqrt{\sum_{k=1}^{M} \left[\hat{p}_i(t_k) - \hat{p}_j(t_k) \right]^2}$$

No more “time”, the data points are now the N^2 distances between each time series

Now, select “neighboring data points” and build adjacency matrix A

What Is L = DM – A ?

Example of how to build A

For each row of D choose the NN nearest neighbors

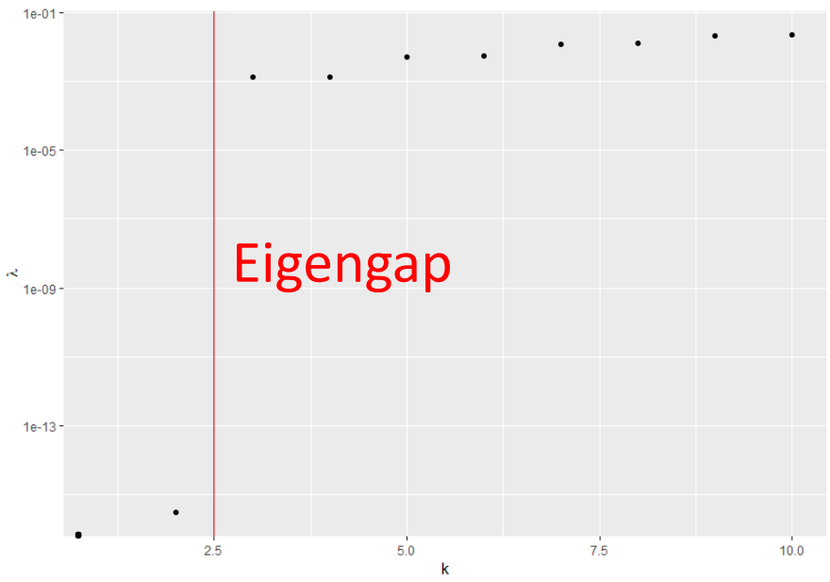
$$D = \begin{bmatrix} 0 & (0.1) & 0.2 & 1.2 & \cdots & 1.4 & (.05) & (.15) & 3.0 \\ \vdots & & & & & & & & \end{bmatrix}$$

$$A = \begin{bmatrix} 0 & 1 & 0 & 0 & \cdots & 0 & 1 & 1 & 0 \\ \vdots & & & & & & & & \end{bmatrix}$$

Define the Degree Matrix DM as a matrix with diagonal elements equal to NN, off-diagonals zero

The Eigengap Heuristic

- Spectral clustering enables calculation of the number of clusters which exist in the data
- K, the number of clusters, can be chosen such that the resulting clusters are robust to small changes in the data
- Compute eigenvalues of L, rank order them and plot



- Look for the “eigengap”
- This defines K
- Determine eigenvectors $\underline{e}_1,..\underline{e}_K$ corresponding to eigenvalues below gap

The Eigengap Heuristic

$$E = \begin{bmatrix} e_{11} & e_{12} & e_{13} & e_{14} \\ e_{21} & e_{22} & e_{23} & e_{24} \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ e_{N1} & e_{N2} & e_{N3} & e_{N4} \end{bmatrix}$$

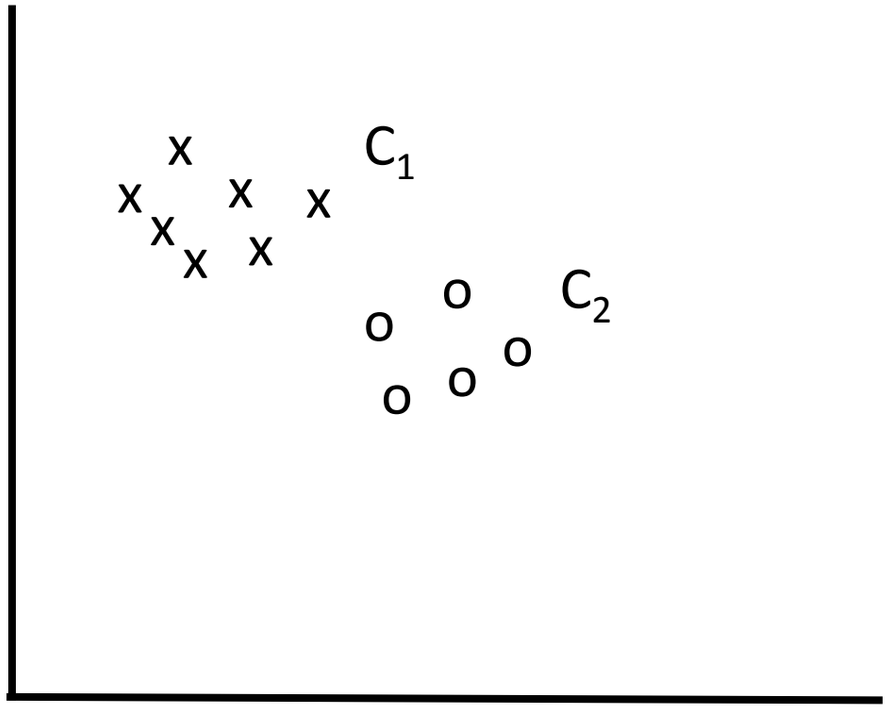
"Membership" of time-series 1 in terms of K clusters

"Membership" of time-series 2 in terms of K clusters

"Membership" of time-series N in terms of K clusters

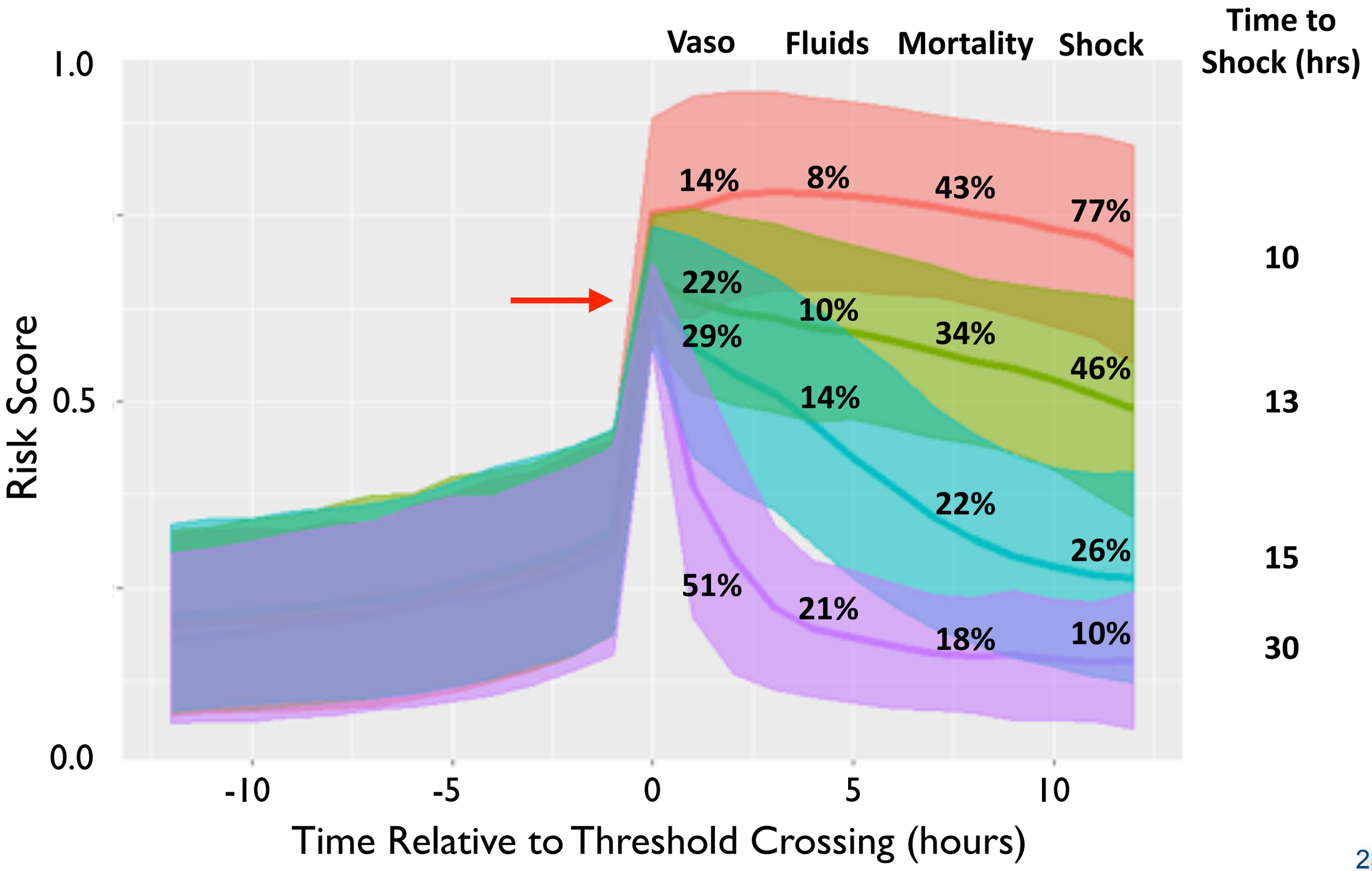
.

Now Cluster the Data



- Typically use K-means clustering to organize data points into clusters
- Cluster membership is then defined. Using cluster membership, calculate average within-cluster risk score over time and plot

How Does Patient Risk Evolve After Detection?



Differences in Physiology and Clinical-Phenotype Between Clusters 1 and 4

Clinical Phenotype and Co-Morbidities:

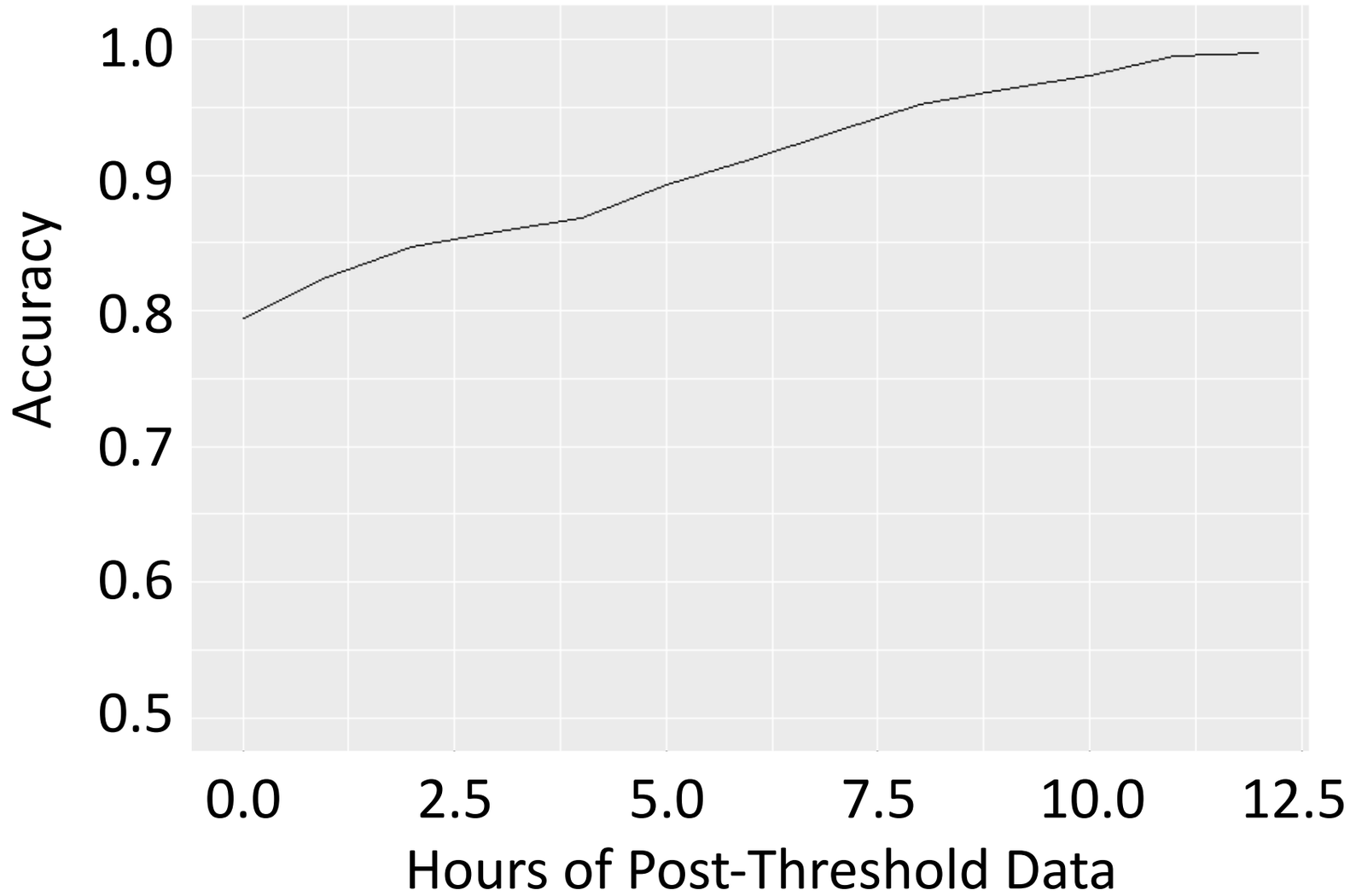
- No differences

Physiology:

- p = 0.01 significance

	Cluster 1	Cluster 4		Cluster 1	Cluster 4
HR	99.4	96.0	**BUN**	39.8	33.2
SBP	107.2	112.4	**pH**	7.30	7.33
DBP	59.3	62.4	**$PaCO_2$**	40.5	41.9
MBP	72.5	75.1	**Urine**	5.6	3.2
Resp	22.7	21.6	**Resp SOFA**	1.1	0.6
FiO_2	66.2%	61.2%	**Nervous SOFA**	0.5	0.3
GCS	12.1	12.8	**Cardio SOFA**	0.4	0.1
Platelets	211.0	232.1	**Liver SOFA**	0.1	0.0
Creatinine	2.2	1.9	**Coag SOFA**	0.5	0.3
Lactate	4.6	2.9	**Kidney SOFA**	1.2	0.8

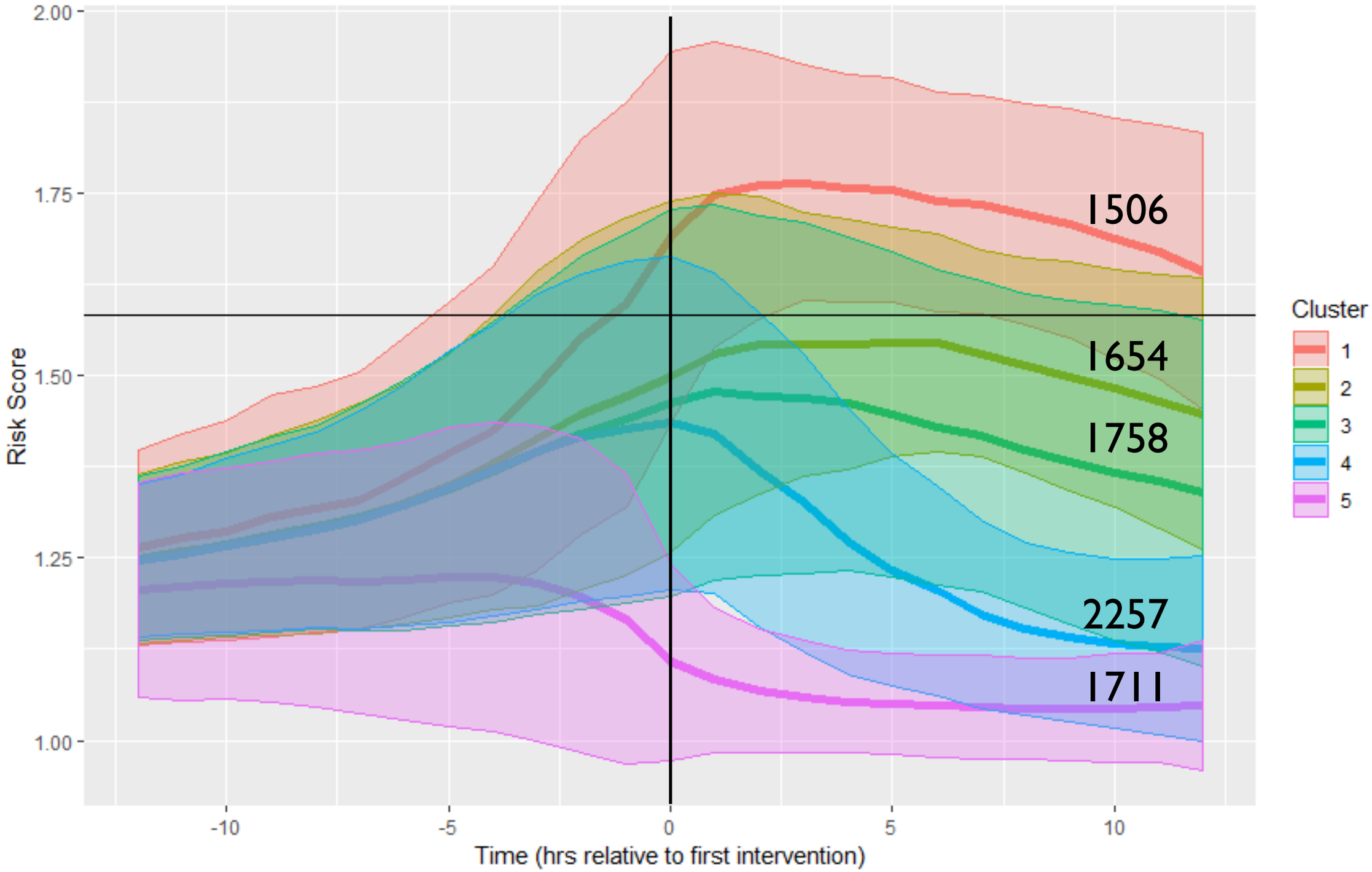
Assigning Patients to Risk-Score Clusters
Cluster 1 Versus Others



Conclusions:

- 80% accuracy immediately using initial data point
- ~90% accuracy by 5 hours
- increasing density of EHR measurements may help

Risk Score Relative to Time of First Intervention



Where We Are Now

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- Fairly reliable early warning of impending septic shock (sensitivity 88%, specificity 84%, AUC .93)
- Median 7 hour early warning time
- patient-specific PPV can be assigned to warning

- There is a dramatic change in risk score that occurs hours before patients are in “shock”
- This change is abrupt, risk changes dramatically in < 1 hour
- I believe the time of this change defines time of entry into septic shock
- Real-time calculation and display of risk score could be very informative to care-givers