

# **Classification Vs. Scores Vs. Staging Vs. Clustering/Phenotyping: *One Better Than The Other?***

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# Disclosure

I, **Mani A. Vannan** **DO NOT** have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

# Mortality Risk of Mild and Moderate TR

## 120,228 patients From The NEDA Database

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### Adverse Prognostic Impact of Even Mild or Moderate Tricuspid Regurgitation: Insights from the National Echocardiography Database of Australia

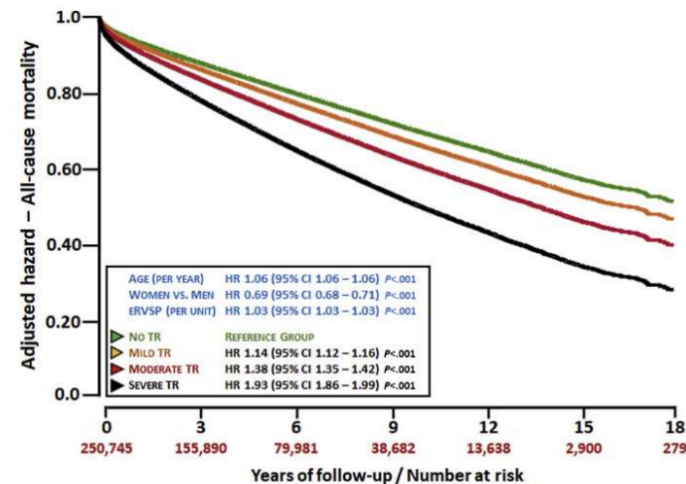
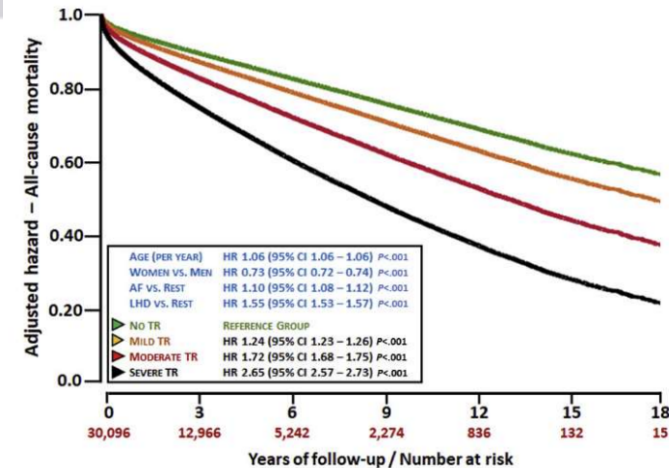
Sophie Offen, MBBS (Hons), BSc, David Playford, MBBS, PhD, Geoff Strange, PhD, Simon Stewart, PhD, and David S. Celermajer, PhD, Sydney, New South Wales; Fremantle, Western Australia; and Adelaide, South Australia, Australia; and Glasgow, Scotland

**Background:** The prevalence and prognostic impact of tricuspid regurgitation (TR) remain incompletely characterized.

**Methods:** The distribution of TR severity was analyzed in 439,558 adults (mean age,  $62.1 \pm 17.8$  years; 51.5% men) being investigated for heart disease, from 2000 to 2019, by 25 centers contributing to the National Echocardiography Database of Australia. Survival status and cause of death were ascertained in all adults from the National Death Index of Australia. The relationship between TR severity and mortality was examined.

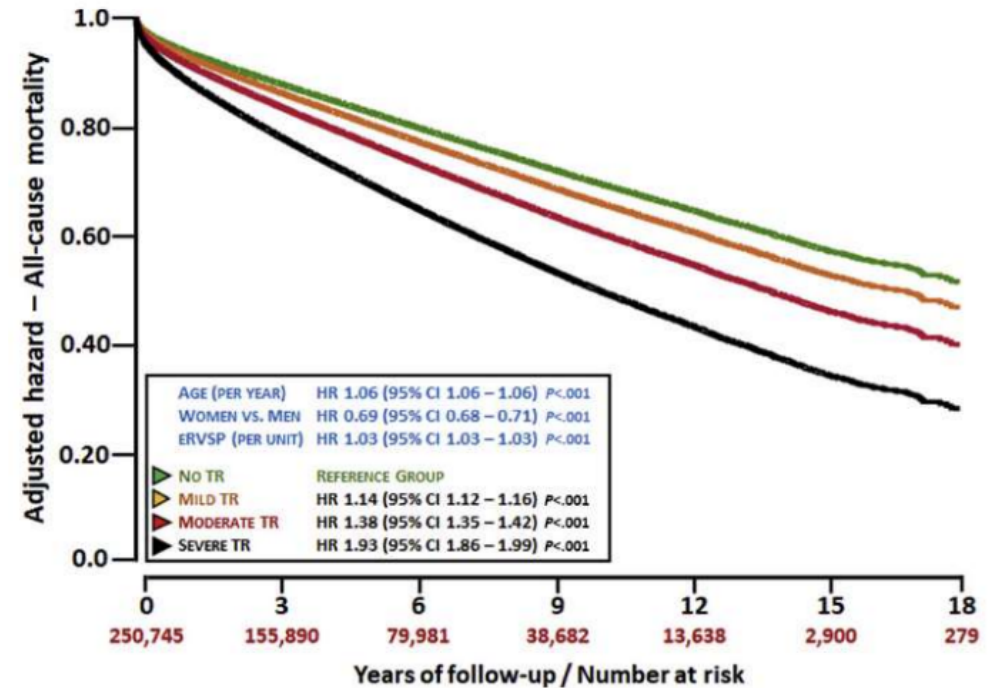
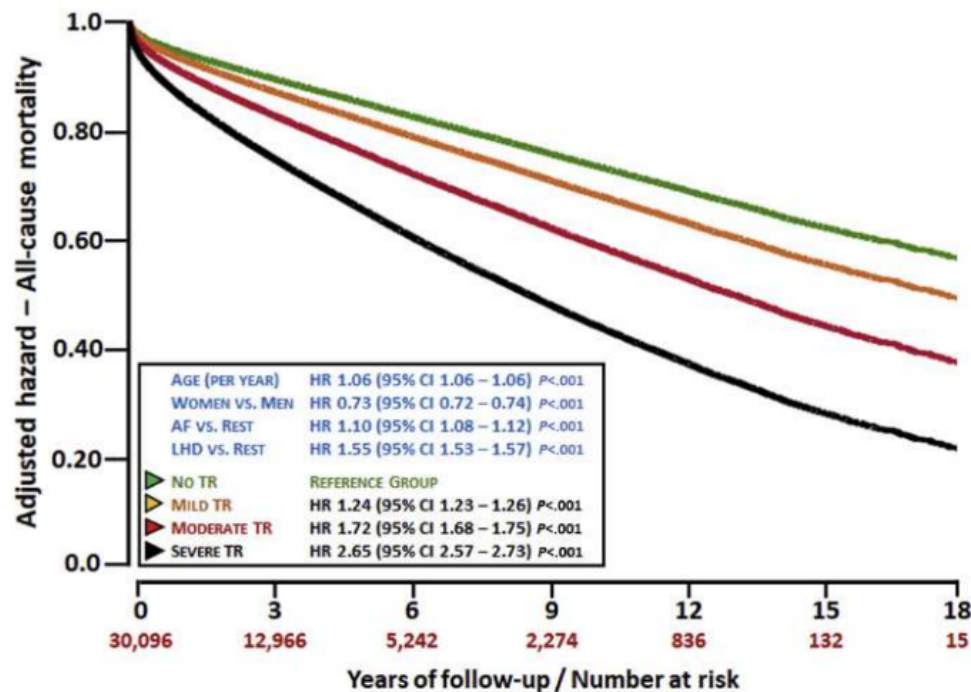
**Results:** Of those studied, 311,604 (70.9%) had no/trivial TR; 94,172 (21.4%), mild TR; 26,056 (5.9%), moderate TR; and 7,726 (1.8%), severe TR. During a median 4.1 years (interquartile range, 2.2-7.0 years) of follow-up, 109,004 died (49% from cardiovascular causes). Moderate or greater TR was associated with older age and female sex ( $P < .001$ ). Individuals with moderate and severe TR had a 2.0- to 3.2-fold increased risk of all-cause long-term mortality after adjustment for age and sex compared with those with no/trivial TR ( $P < .001$  for both comparisons). Even those with mild TR had a significantly increased risk for mortality (hazard ratio [HR] = 1.29; 95% CI, 1.27-1.31). In fully adjusted models, including for RV systolic pressure, atrial fibrillation, and significant left heart disease, there remained a 1.24- to 2.65-fold increased risk of mortality with mild (HR = 1.24; 95% CI, 1.23-1.26), moderate (HR = 1.72; 95% CI, 1.68-1.75), or severe TR (HR = 2.65; 95% CI, 2.57-2.73), compared with those with no/trivial TR ( $P < .001$  for all).

**Conclusions:** Tricuspid regurgitation is a common condition in adults referred for echocardiography. Moreover, even in the presence of other cardiac disease, increasing grades of TR are independently associated with increasing risks of cardiovascular and all-cause mortality. Furthermore, we show that even mild TR is independently associated with a significant increase in mortality. (J Am Soc Echocardiogr 2022; ■: ■-■.)



# Mortality Risk of Mild and Moderate TR

120,228 patients From The NEDA Database



# LaPar (Michigan/ Virginia) Score

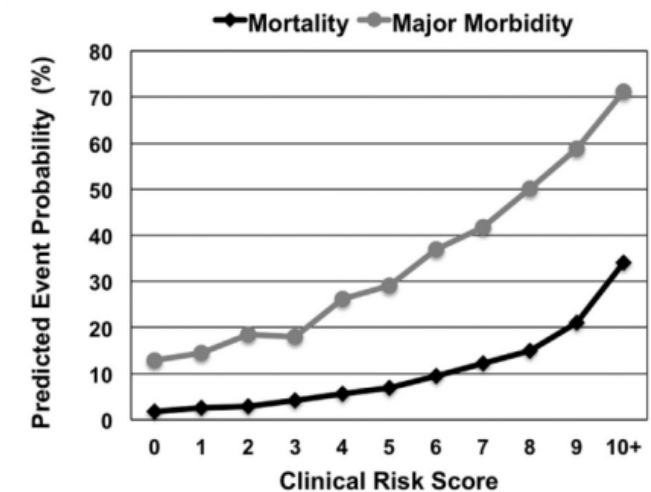
Isolated TV Surgery, 2050 patients in 50 Hospitals (2002-2014)

Multivariable Logistic Regression Analysis for Outcome of Operative Mortality

Factor	OR <sub>adj</sub>	95% CI		p Value	CRS Value
		LL	UL		
Age, years, versus <40					
60-69	2.26	1.15	4.45	0.02	2
70+	3.27	1.7	6.29	0.001	3
Female	1.41	1.02	1.96	0.04	1
Stroke	2.03	1.29	3.2	0.002	2
Hemodialysis	3.34	2.09	5.33	<0.001	4
Chronic lung disease, versus none					
Moderate	1.56	0.93	2.63	0.09	1
Severe	3.04	1.86	5	<0.001	3
NYHA class, versus class I/II					
III	2.05	1.12	3.76	0.02	2
IV	3.33	1.8	6.16	0.001	3
Reoperation	1.59	1.15	2.19	0.005	2
Status, emergent	4.37	2.04	8.99	<0.001	4
Intercept	0.009	0.004	0.02	<0.001	...

CI = confidence interval; CRS = clinical risk score; LL = lower limit; NYHA = New York Heart Association; OR<sub>adj</sub> = adjusted odds ratio; UL = upper limit.

Patient Factor	Mortality CRS	Major Morbidity CRS	Example Case
Age (years)			73 yo, female, moderate lung disease, NYHA Class III
50-59	0	1	
60-69	2	2	
70+	3	2	<b>Total Mortality CRS:</b> 3 + 1 + 1 + 2 = 7
Sex (Female)	1	1	
Stroke	2	1	<b>Total Major Morbidity CRS:</b> 2 + 1 + 1 + 2 = 6
Hemodialysis	4	1	
Chronic Lung Disease			<b>Predicted Mortality = 12%</b> (from graph below)
Moderate	1	1	
Severe	3	1	
Ejection Fraction < 55%	0	2	<b>Predicted Major Morbidity = 37%</b> (from graph below)
NYHA Class			
Class III	2	2	
Class IV	3	3	
Reoperation Status			
Emergent	4	9	



LaPar D *et al.* Investigators for the Virginia Cardiac Surgery Quality Initiative and the Michigan Society of Thoracic and Cardiovascular Surgeons. Development of a Risk Prediction Model and Clinical Risk Score for Isolated Tricuspid Valve Surgery. *Ann Thorac Surg.* 2018;106:129-136

# Tri-Score

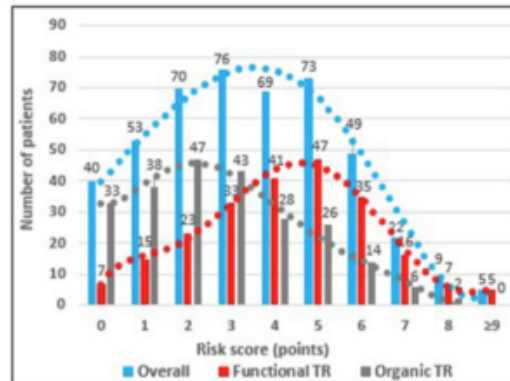
## Isolated TV Surgery

All consecutive adult patients who underwent an isolated tricuspid valve surgery for severe tricuspid regurgitation at 12 French centers between 2007 and 2017 (N=466)

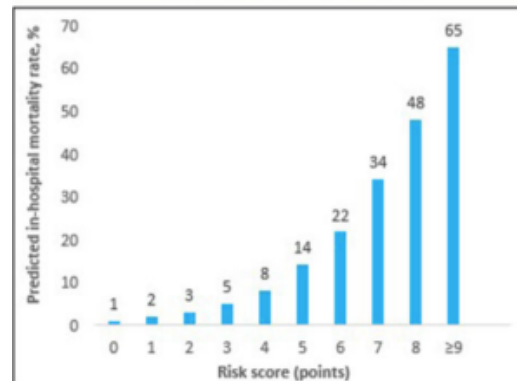
### Risk factors and scoring system for in-hospital mortality after isolated tricuspid valve surgery

Risk factors (final model from multivariate analysis)	Scoring
Age ≥ 70 years	1
NYHA functional class III-IV	1
Right-sided heart failure signs	2
Daily dose of furosemide ≥ 125mg	2
Glomerular filtration rate < 30 ml/min	2
Elevated total bilirubin	2
Left ventricular ejection fraction < 60%	1
Moderate/severe right ventricular dysfunction	1
<b>Total</b>	<b>12</b>

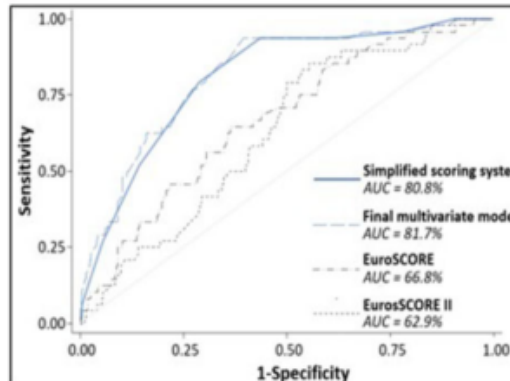
### Number of patients presenting with each score value and trends



### Predicted in-hospital mortality rate according to the final risk score model



### Receiver operating characteristic curves



Dreyfus J et al., TRI-SCORE: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. Eur Heart J. 2022 ;43:654-662

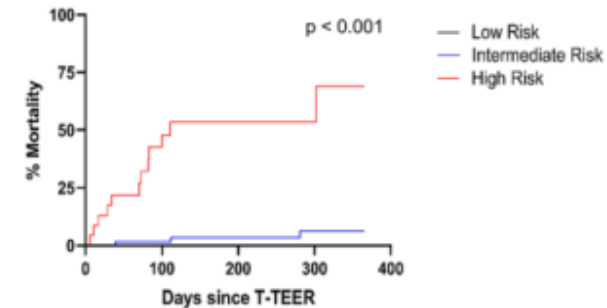
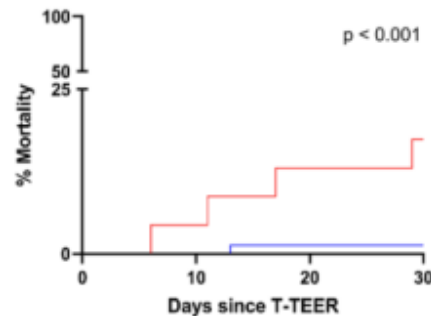
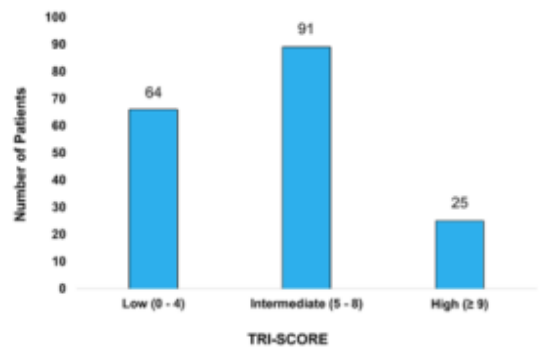
# Comparison of TV Risk Scores

Tri-Score Vs. EuroScore II and STS Score, 180 patients, TV Clip, Single Center

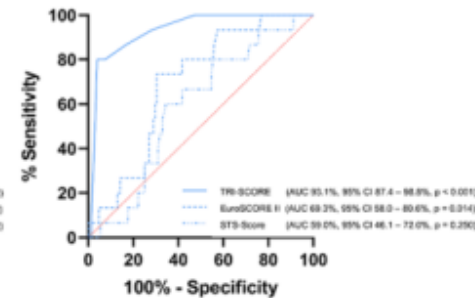
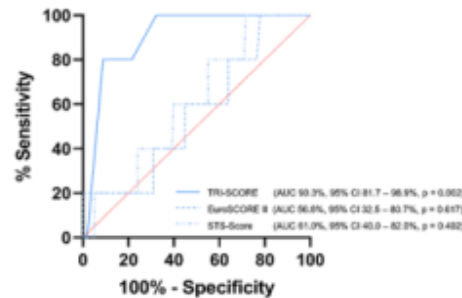
180 patients who underwent transcatheter edge-to-edge tricuspid valve repair retrospectively analyzed

Stratification into TRI-SCORE groups

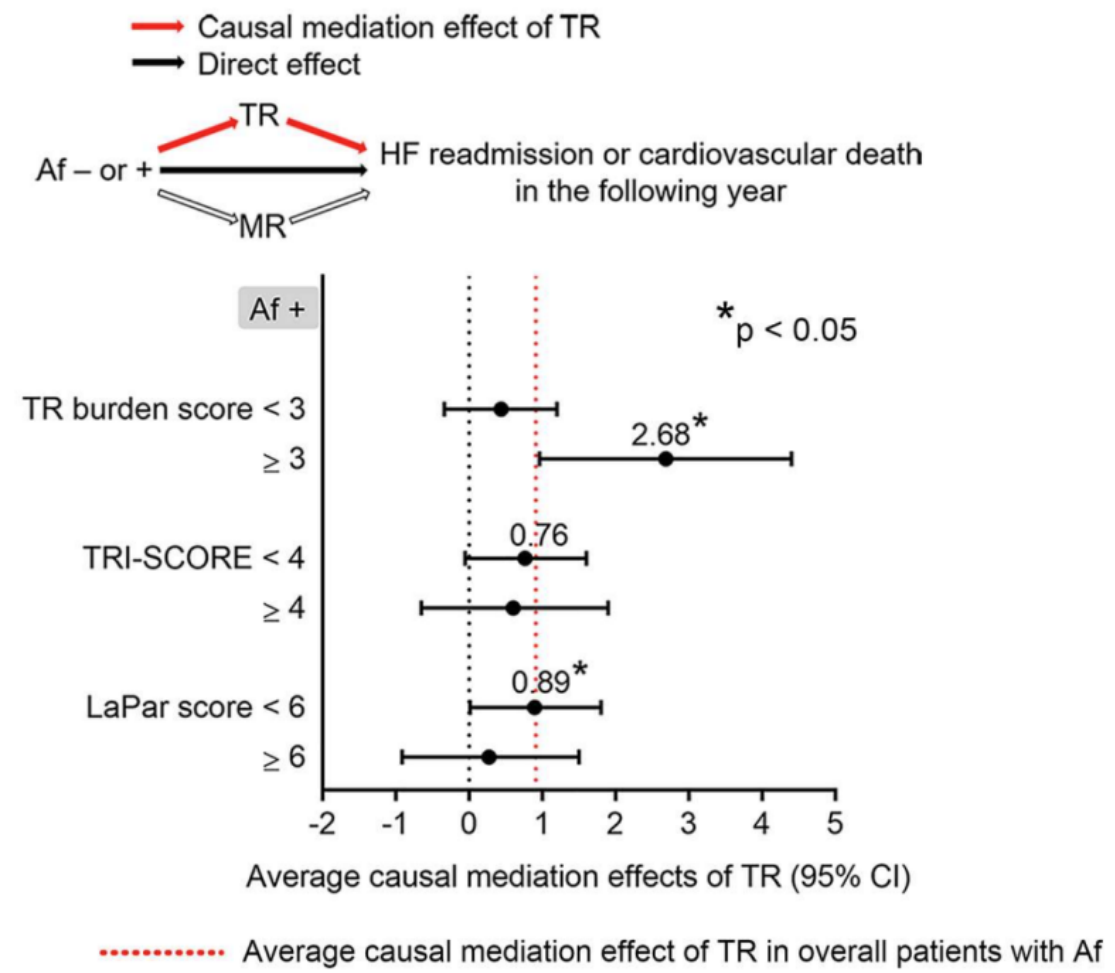
30 day and up to one year mortality



Receiver operating characteristic curves of TRI-SCORE compared to EuroSCORE II and STS-Score for prediction of 30 day and mid-term mortality



# TR Scores: 1 Year HF Readmission and CV Death



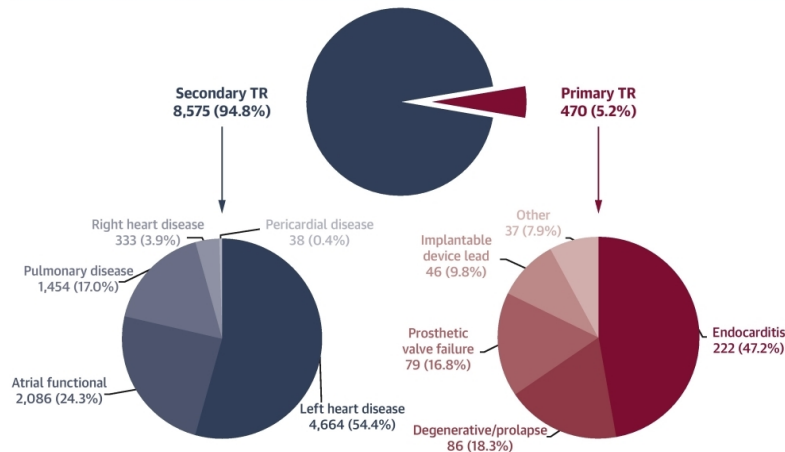


# “Novel” (Cleveland Clinic) Score

9,045 Patients,  $\geq$ Moderate TR on Echo, 60% Women, 2004-2018

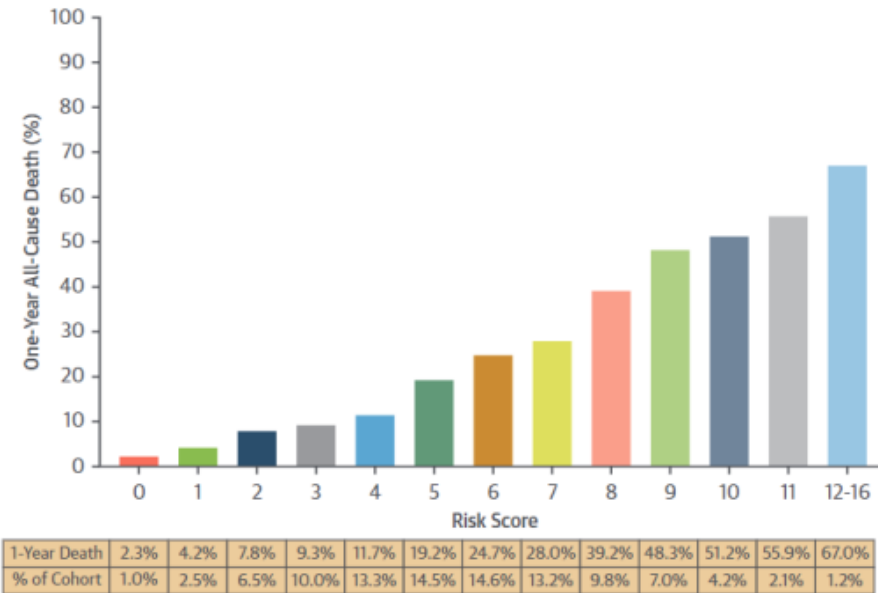
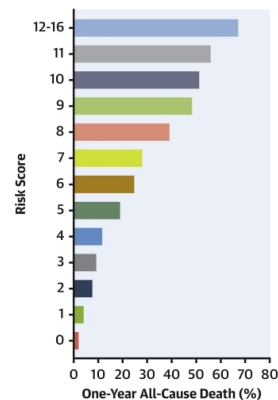
## CENTRAL ILLUSTRATION: Classification of Isolated Tricuspid Regurgitation Etiologies and Novel Risk Score for 1-Year Mortality

### Etiological Classification for Isolated Severe TR



### Risk Model for 1-Year All-Cause Mortality in Isolated Secondary TR

Parameter	Score
Age	
65-74 years	1
75+ years	2
Myocardial infarction	1
Peripheral vascular disease	1
Chronic lung disease	1
Chronic kidney disease (creatinine >1.4 mg/dL)	1
Loop diuretic use	1
Anemia (hemoglobin <10 g/dL)	1
Thrombocytopenia (platelet <15 k/ $\mu$ L)	1
International normalized ratio >1.5	1
Albumin <3.0 g/dL	2
Right ventricle systolic function	
Mildly impaired	1
Moderately impaired	2
Severely impaired	3
Right ventricular systolic pressure >50 mm Hg	1
Total score	16

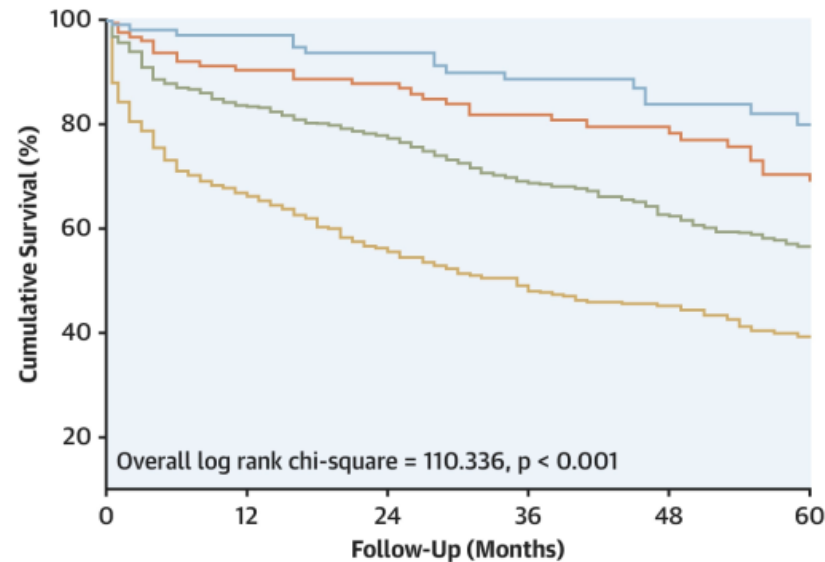


Plot of 1-year all-cause mortality rate in isolated secondary tricuspid regurgitation by the novel risk score.

# Staging RV Function in TR

1,311 Patients, Significant TR, RHF

## CENTRAL ILLUSTRATION: Kaplan-Meier Curves for Survival According to Stages of Right Heart Failure



Number at risk

	0	12	24	36	48	60
Stage 1	101	94	79	63	48	41
Stage 2	124	110	96	77	63	51
Stage 3	683	566	472	356	268	202
Stage 4	403	266	197	146	111	77

### Stage 1

(n=101)

- At risk for right heart failure without RV dysfunction and without signs/symptoms of right heart failure

### Stage 2

(n=124)

- RV dysfunction without signs/symptoms of right heart failure

### Stage 3

(n=683)

- RV dysfunction with prior or current signs/symptoms of right heart failure

### Stage 4

(n=403)

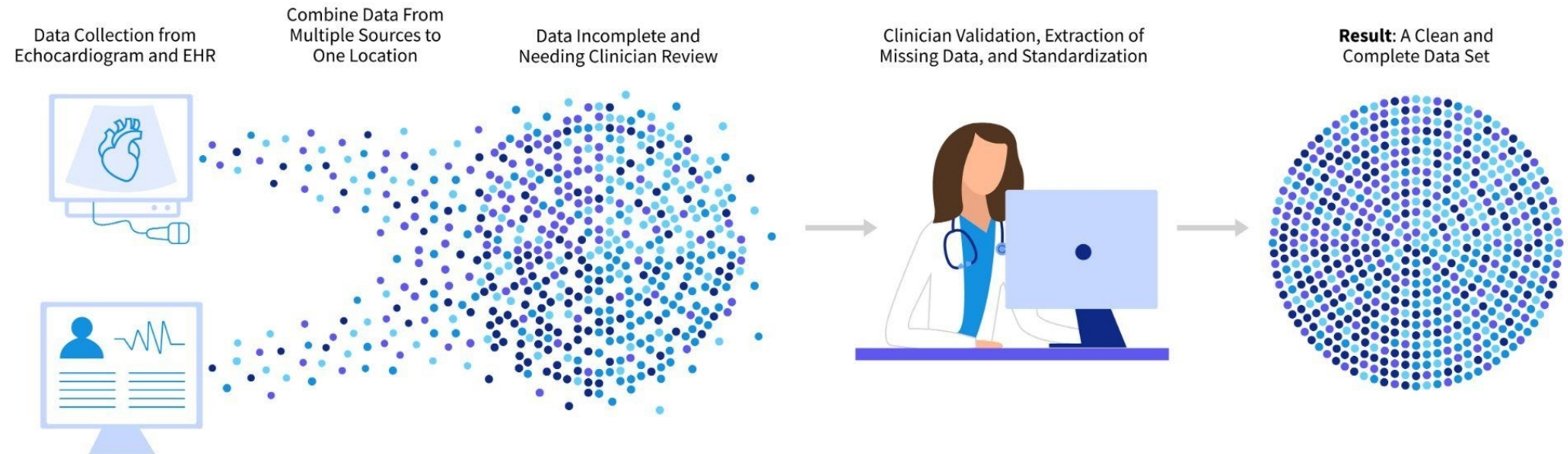
- RV dysfunction with refractory signs/symptoms of right heart failure at rest (requiring specialized interventions)

RV-function	NYHA class	Diuretics	Edema
TAPSE $\geq$ 17	I	-	-
TAPSE<17	I	-	-
TAPSE<17	II-III	+	-
TAPSE<17	IV	+	+

# FTR M-L Clusters (Phenotypes)

856 patients with Moderate to Severe and Severe TR

## Data Collection, Clean, and Prep

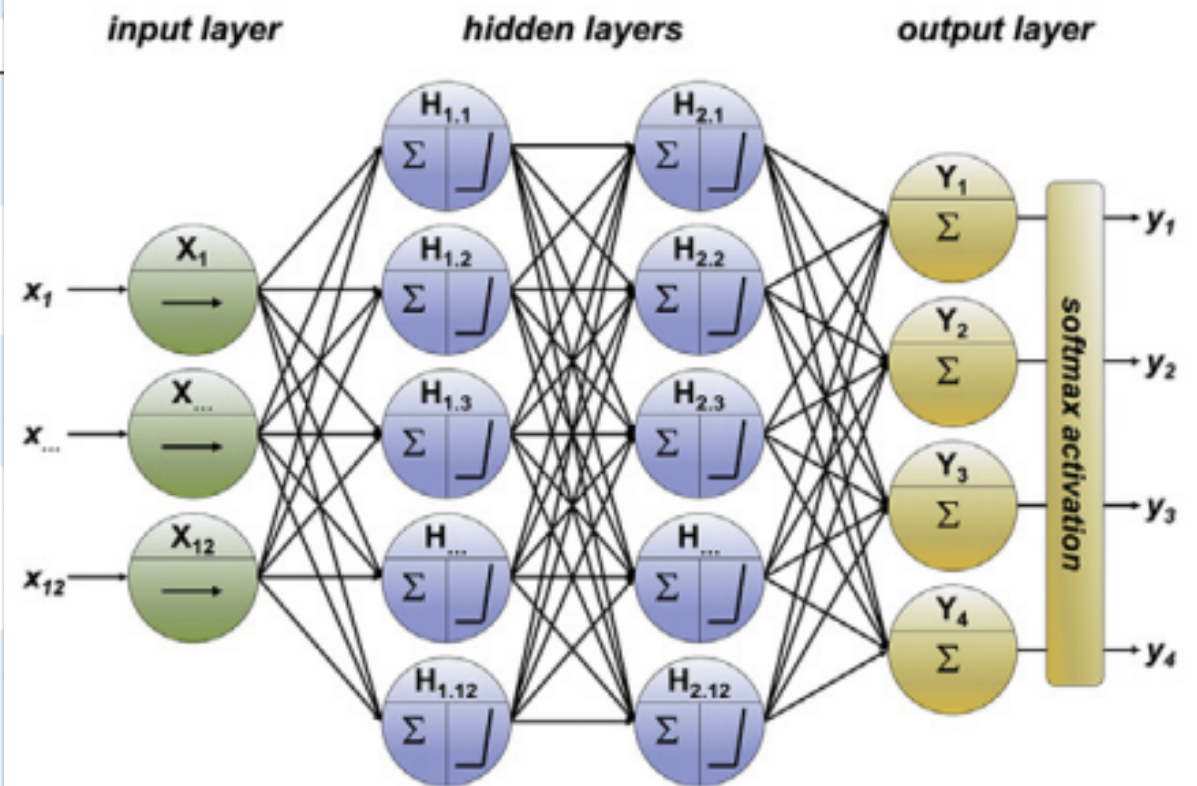


# Staging Vs. M-L Based Clustering

## Multivariable Analysis Vs. Clinical Phenotypes

**TABLE 3 Incremental Prognostic Value of the Modified Staging Classification**

	NRI	p Value
Multivariable model including: Original staging classification*	Referent	
Modified staging classification	0.25	0.02
Multivariable model including: Age	Referent	
Modified staging classification	0.30	0.006
Multivariable model including: $V_{peak}$	Referent	
Modified staging classification	0.33	0.003
Multivariable model including: Original staging classification*, age, sex, logistic EuroSCORE, and $V_{peak}$	Referent	
Modified staging classification	0.35	0.002
Multivariable model including: Original staging classification*, age, sex, BMI, logistic EuroSCORE, hypertension, diabetes mellitus, and $V_{peak}$	Referent	
Modified staging classification	0.34	0.003



Tastet L et al., J Am Coll Cardiol 2019;74:550-63

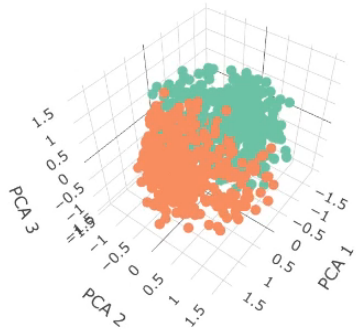
# FTR M-L Clusters (Phenotypes)

856 patients with Moderate to Severe and Severe TR

3D KMedoids Cluster plot

44-Variate KMedoids Assigned Clust

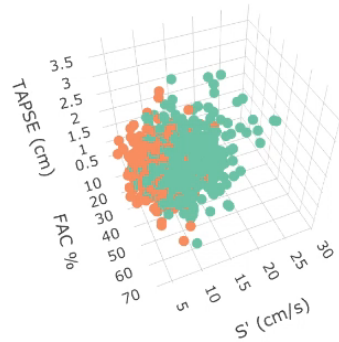
- 1
- 2



3D KMedoids Cluster plot

44-Variate KMedoids Assigned Cluster

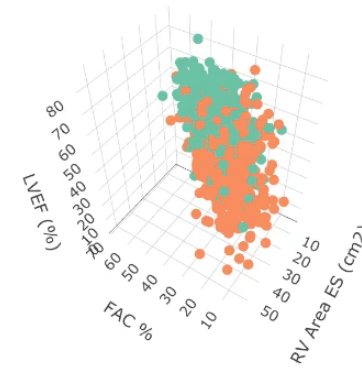
- 1
- 2

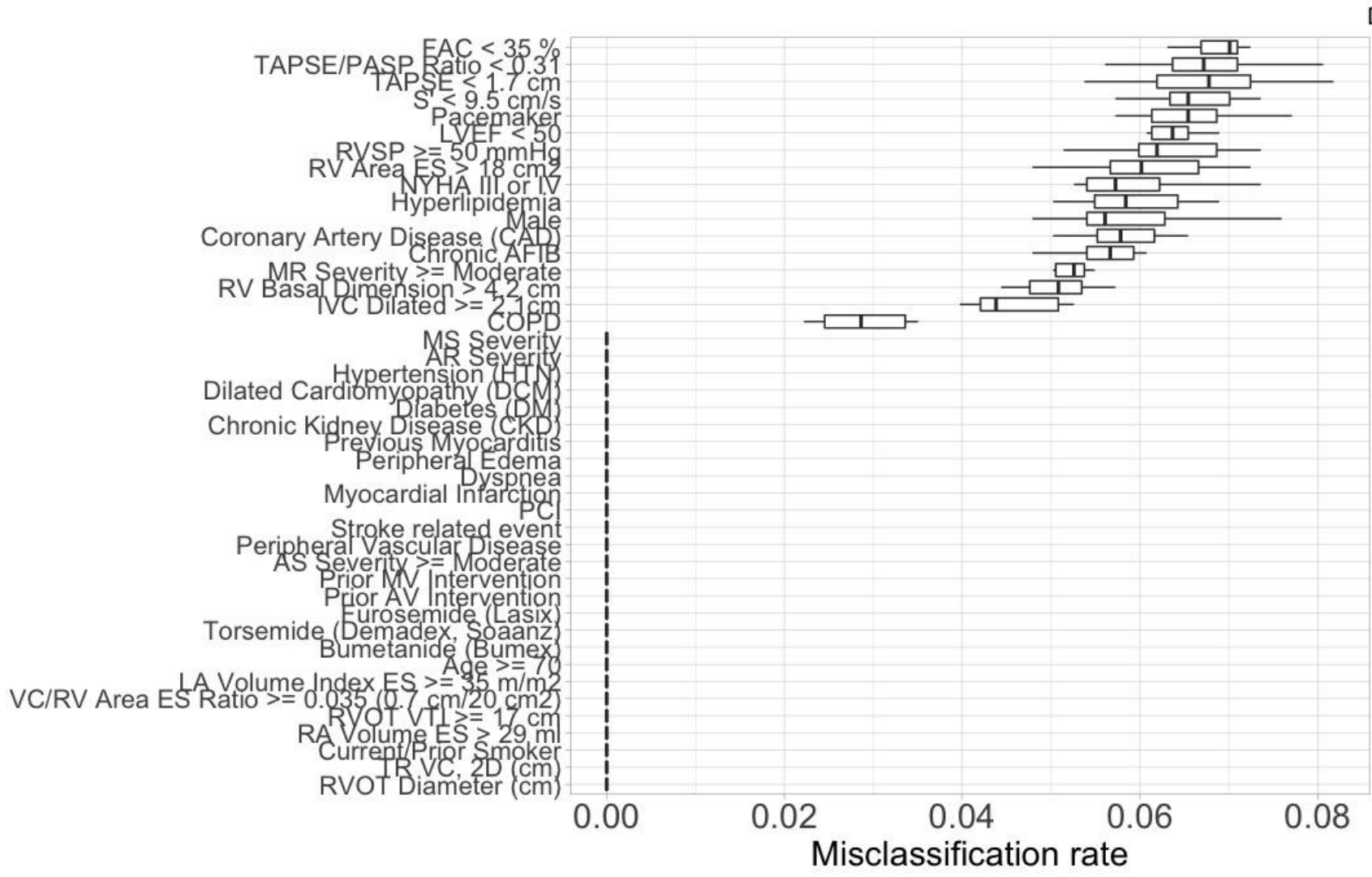


3D KMedoids Cluster plot

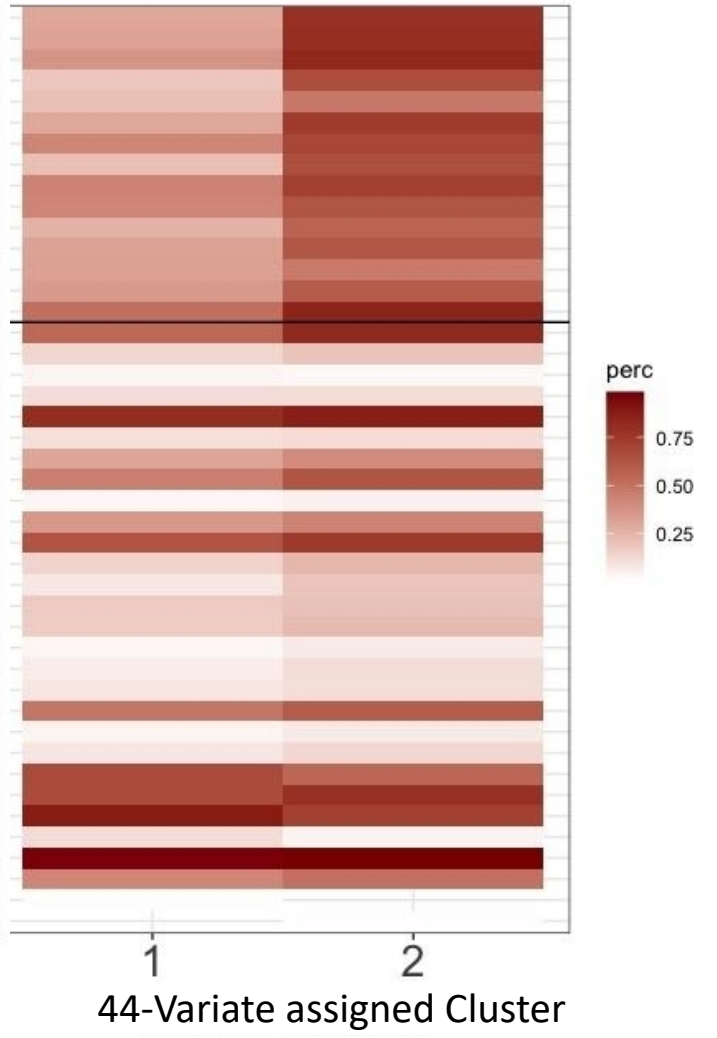
44-Variate KMedoids Assigned Cluster

- 1
- 2



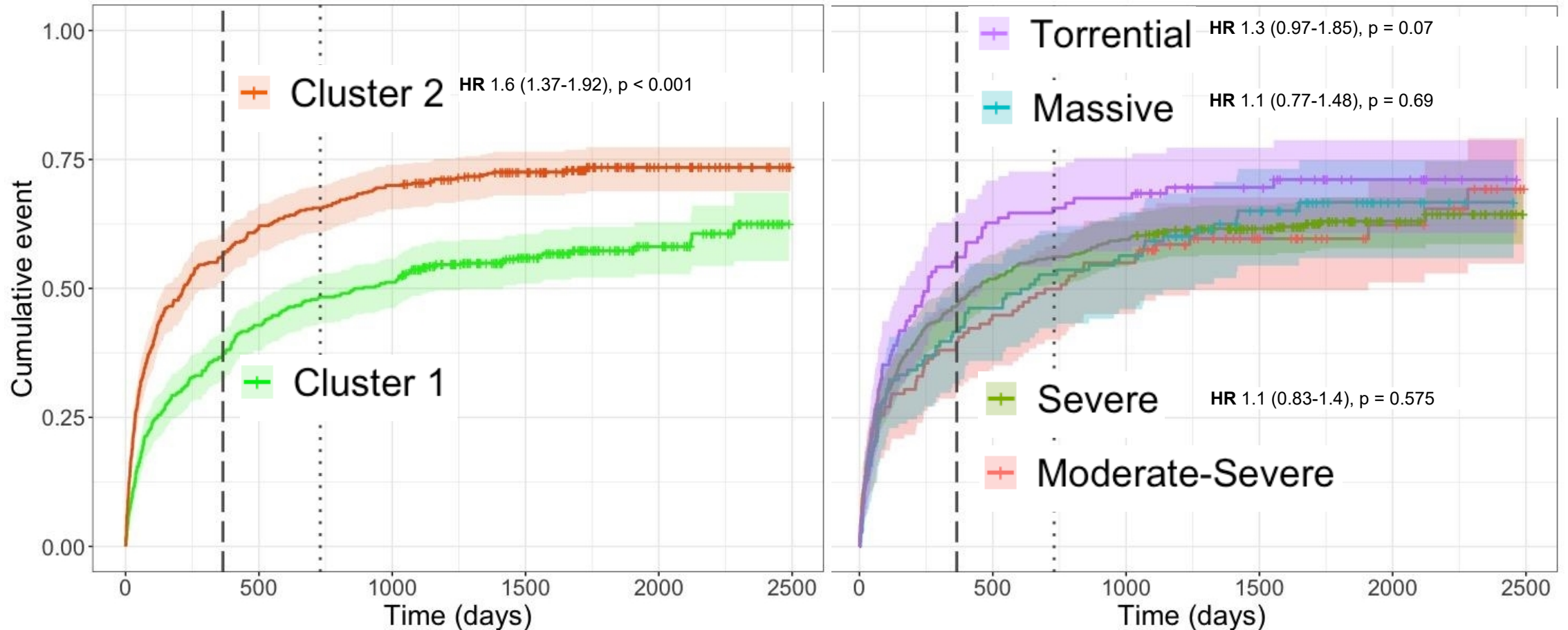


Distribution of characteristics across clusters

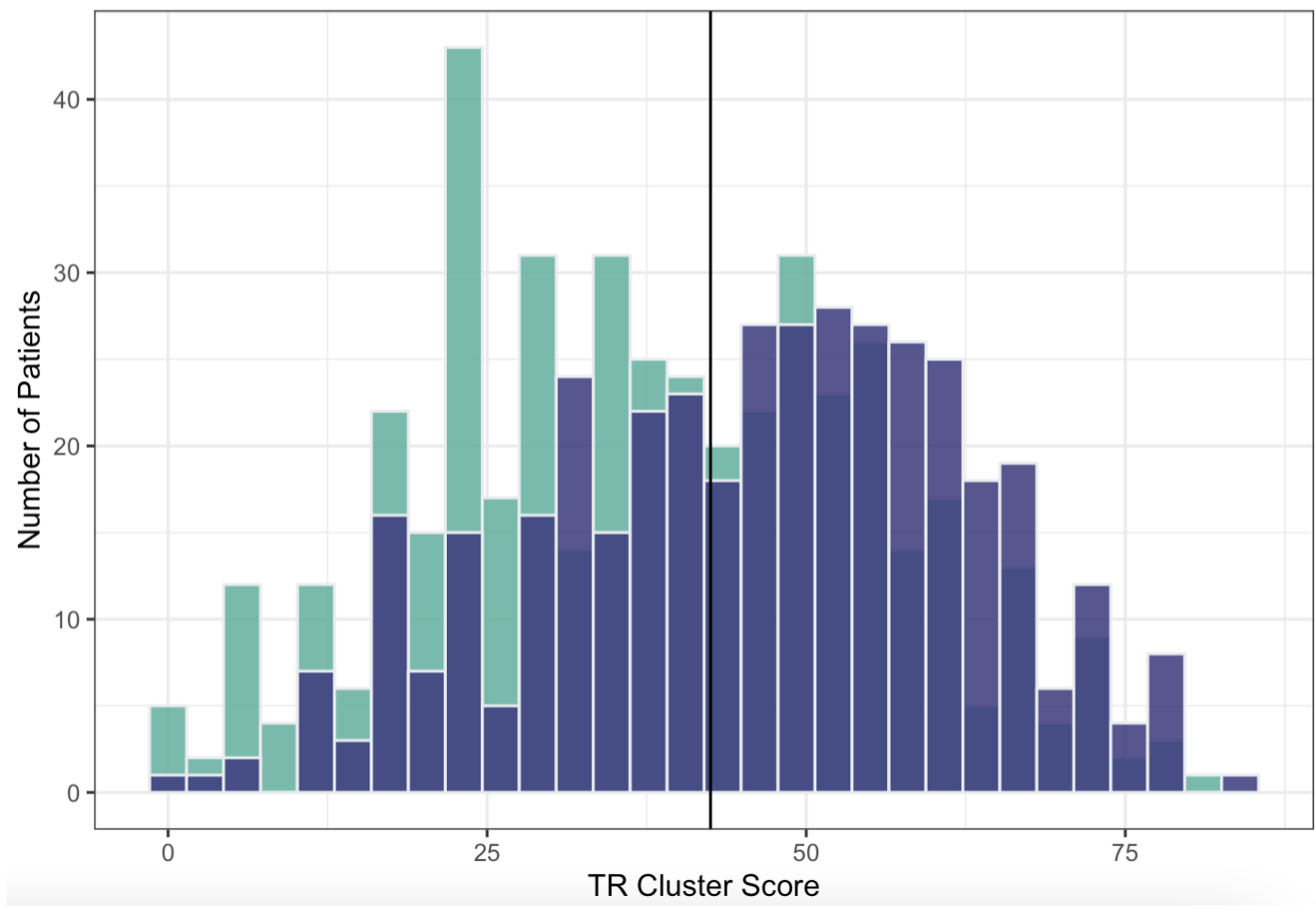


# Mortality Risk of FTR M-L Clusters (Phenotypes)

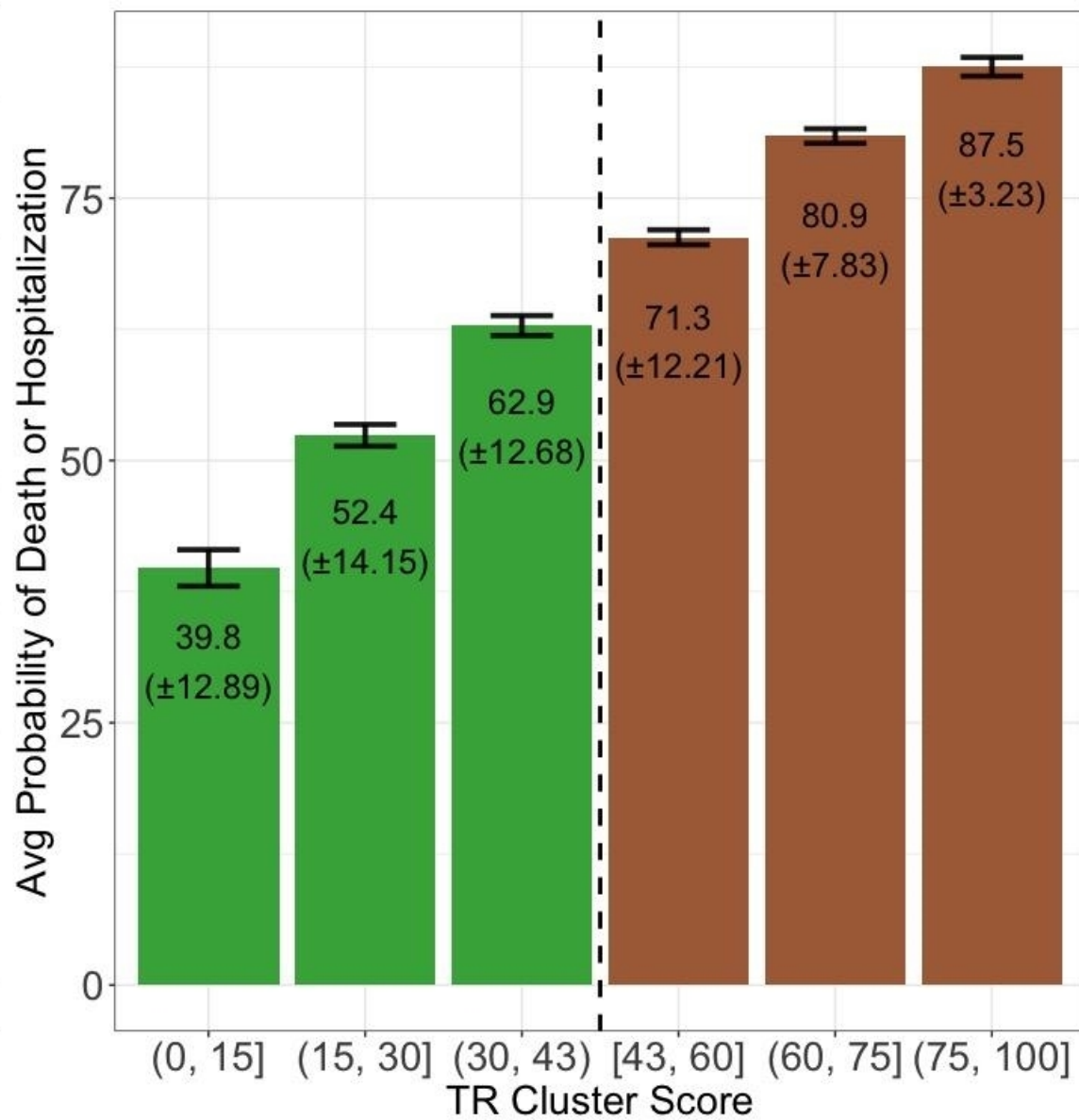
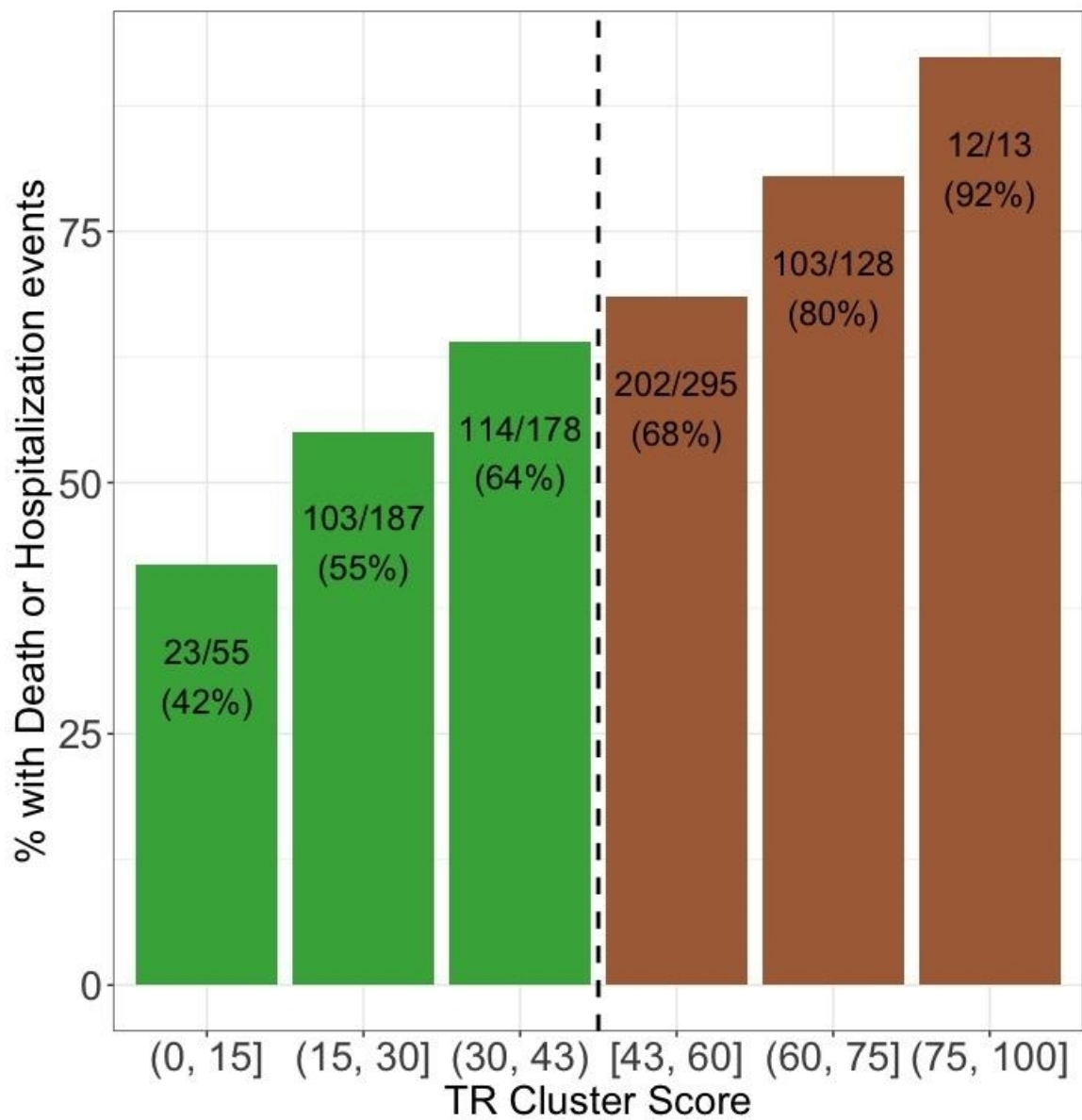
856 patients with Moderate to Severe and Severe TR



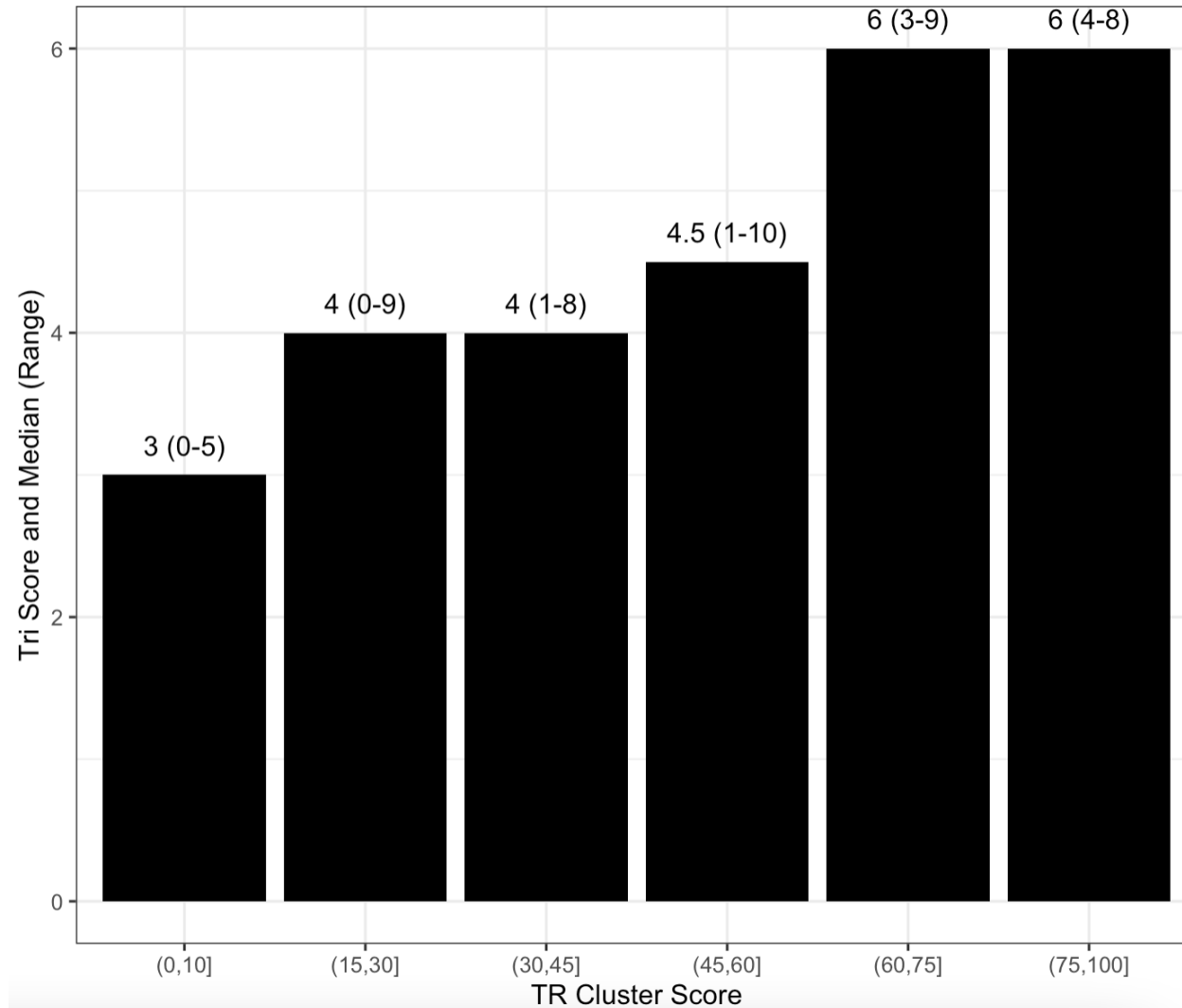
Not Deceased nor Hospitalized within 1 year    Deceased or Hospitalized within 1 year







# Tri Score and the TR Clustering Score





# Conclusions

- **Classification** of the severity of valve lesion is NOT sufficient in clinical decision-making
- **The Scoring/Staging** approach provided the “stage” for evolution of machine-learning (ML) clustering algorithms
- **ML clustering-based phenotypes** of the disease may yet be the most optimal approach in clinical decision-making
- **“The greatest benefit of machine learning may ultimately be not what the machines learn but what we learn by teaching them.”** (*The Master Algorithm: How the Quest for the Ultimate Learning Machine Will Remake Our World*)