Clinical and Echocardiographic Predictors of Mortality in Patients with Severe Tricuspid Valve Regurgitation

Olga Dankevich BSc, Diab Mutlak MD, Shemy Carasso MD, Jonathan Lessick MD Dsc, Izhak Kehat MD PhD, Doron Aronson MD Shimon A. Reisner MD, Yoram Agmon MD

Echocardiography Laboratory and Heart Valves Clinic
Rambam Health Care Campus
Technion – Israel Institute of Technology
Haifa

IHS 60th Annual Scientific Meeting

Apr 22 2013, Jerusalem

Conflicts of interest – **none** (all coauthors)

Background

- Tricuspid valve regurgitation (TR) is a common valve lesion which is frequently misdiagnosed and occasionally ignored clinically
- Limited data for pts with severe TR:
  - Spectrum of disease (clinical / echocardiographic characteristics)
  - Clinical outcome[1]
  - Risk factors for adverse outcome

Nath J et al, *JACC* 2004;43:405-9

Objectives

- To describe the clinical and echocardiographic characteristics in a large group of consecutive pts with severe TR examined at a tertiary medical center
- To evaluate the survival of patients with severe TR during intermediate-term follow-up
- To determine the clinical and echocardiographic risk factors associated with mortality in pts with severe TR

Methods

Patient Population & Data Collection

- Identification of consecutive pts with severe TR
  - Echocardiography laboratory computerized database (3 yrs)
  - Echocardiographic Dx of severe TR (ASE criteria)
  - Pts with multiple exams with severe TR – analysis of 1st exam

- Abstracting of data
  - Review of echocardiography reports
  - Review of hospital medical records (subgroup of hospitalized pts)
- Mortality data
  - Ministry of Interior computerized database

Statistical Analysis

- Comparison of survival between pt subgroups
  - Kaplan-Meier (Log-rank statistics)
- Risk factors for mortality – Cox proportional hazards models

  All models – *adjusted* for age, gender, hospitalization status
  - Stage I: Adjusting variables + echocardiographic parameters (all pts)
  - Stage II: Stage I + clinical variables (subgroup of hospitalized pts)

Results
Clinical Characteristics

Variable	All pts (n=341)	Hospitalized (n=239)	Non-hosp. (n=102)	*P*
Age, yrs	73±14	74±14	71±13	0.03
Male, n (%)	124 (36)	97 (41)	27 (27)	0.01
Atrial fibrillation, n (%)	218 (64)	146 (61)	72 (71)	0.09
Pacemaker, n (%)	85 (25)	56 (23)	29 (28)	0.33
Rheumatic heart disease, n (%)	56 (16)	24 (10)	32 (31)	<0.001
Aortic / mitral surgery – per Hx, n (%)	107 (31)	56 (23)	51 (50)	<0.001
Cardiac hospitalization, n (%)		170 (71)		
NYHA III-IV, n (%)		136 (57)		
Anasarca / ascites, n (%)		88 (37)		
Charlson co-morbidity index*		3 (1-5)		

* Median values (25-75% range)

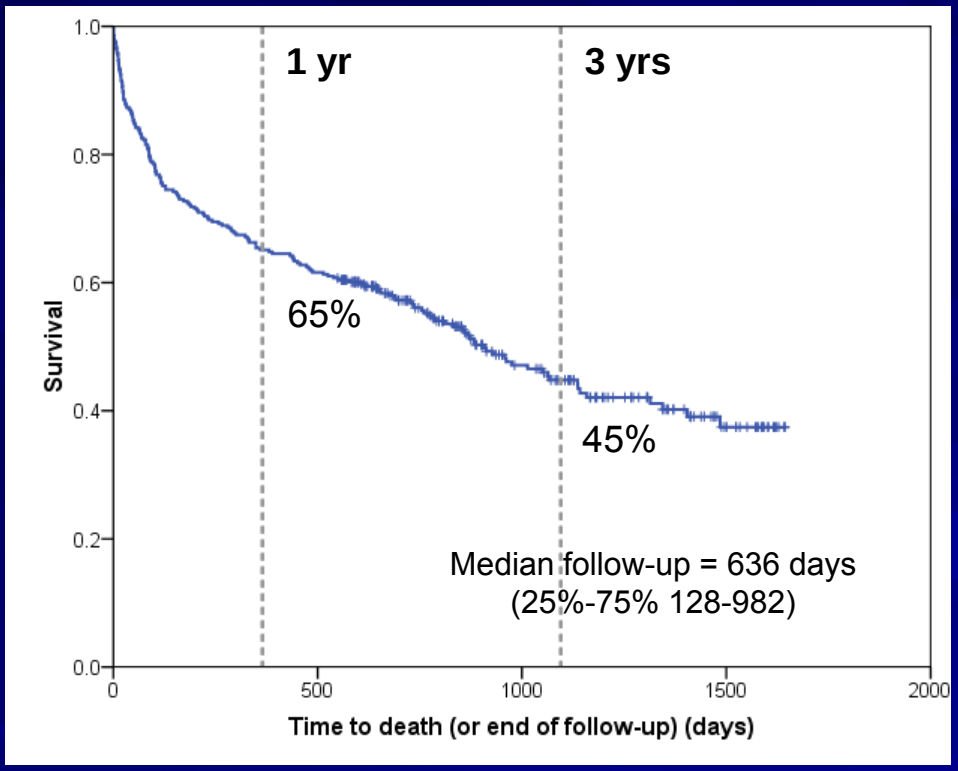
Echocardiographic Characteristics

Variable	All pts (n=341)	Hospitalized (n=239)	Non-hosp. (n=102)	*P*
LVEF, %	52±17	50±18	57±13	<0.001
Mitral regurgitation*, n (%)	126 (37)	93 (39)	33 (32)	0.25
Organic tricuspid valve disease†, n (%)	35 (10)	19 (8)	16 (16)	0.03
Tricuspid valve malcoaptation, n (%)	88 (26)	61 (26)	27 (27)	0.86
RV enlargement*, n (%)	121 (36)	91 (38)	30 (29)	0.13
RV dysfunction*, n (%)	68 (20)	63 (26)	5 (5)	<0.001
RA enlargement*, n (%)	177 (52)	113 (47)	64 (63)	<0.01
PA pressure, mmHg	58±16	60±16	55±14	0.02
RA pressure, mmHg	16±5	16±5	16±5	0.5

* Moderate or severe; † including pts with failed tricuspid annuloplasty

Survival

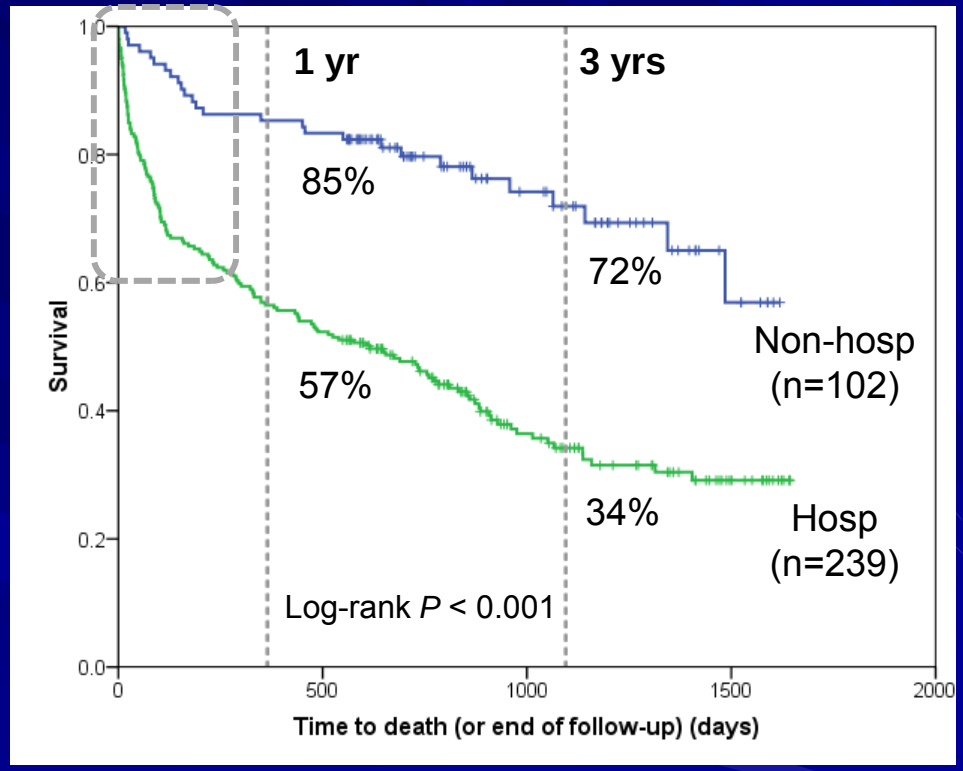
All patients



No. at risk

Baseline	1 yr	3 yrs
341	222	72

By hospitalization status



No. at risk

	Baseline	1 yr	3 yrs
Hosp	239	135	42
Non-hosp	102	87	30

Echocardiographic* Predictors of Mortality

Total Population – Multivariate Cox Regression

Variables	HR	95% CI	*P*
Basic adjusting variables			
Age, per 10 yrs	1.28	1.11-1.47	<0.001
Male	1.34	0.99-1.83	0.06
Hospitalized (during index echo)	2.34	1.52-3.59	<0.001
Additional significant variables			
RV dysfunction ≥ moderate	1.81	1.25-2.61	0.002
PA pressure, per 10 mmHg	1.25	1.15-1.37	<0.001

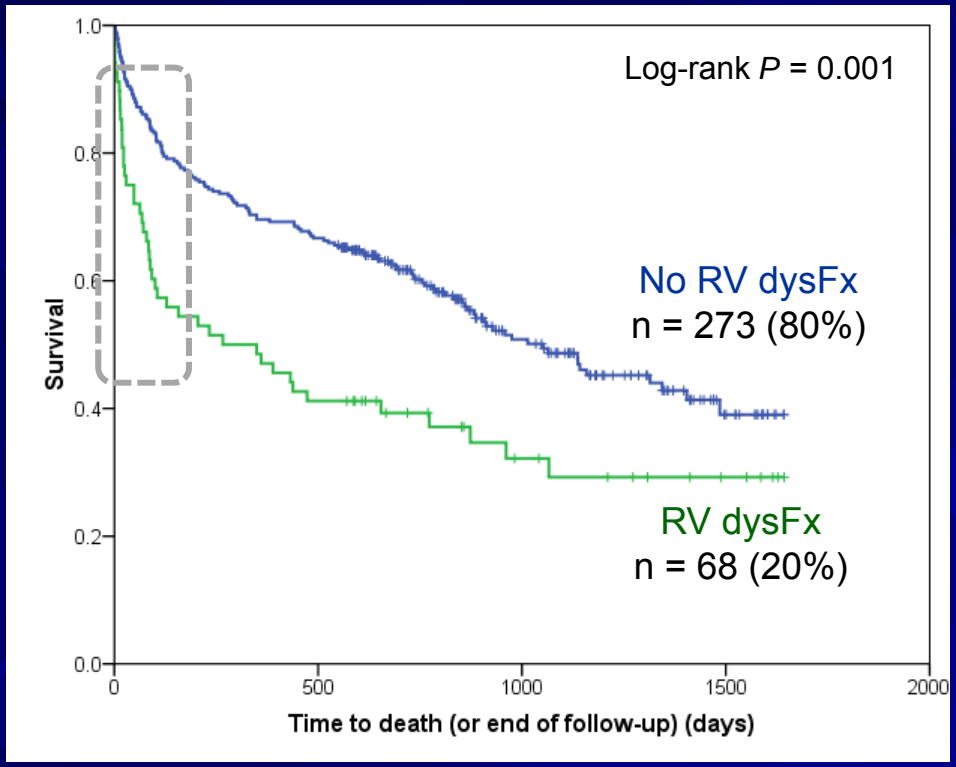
* + Limited # of clinical variables (available in all pts)

Non-significant predictors of mortality:

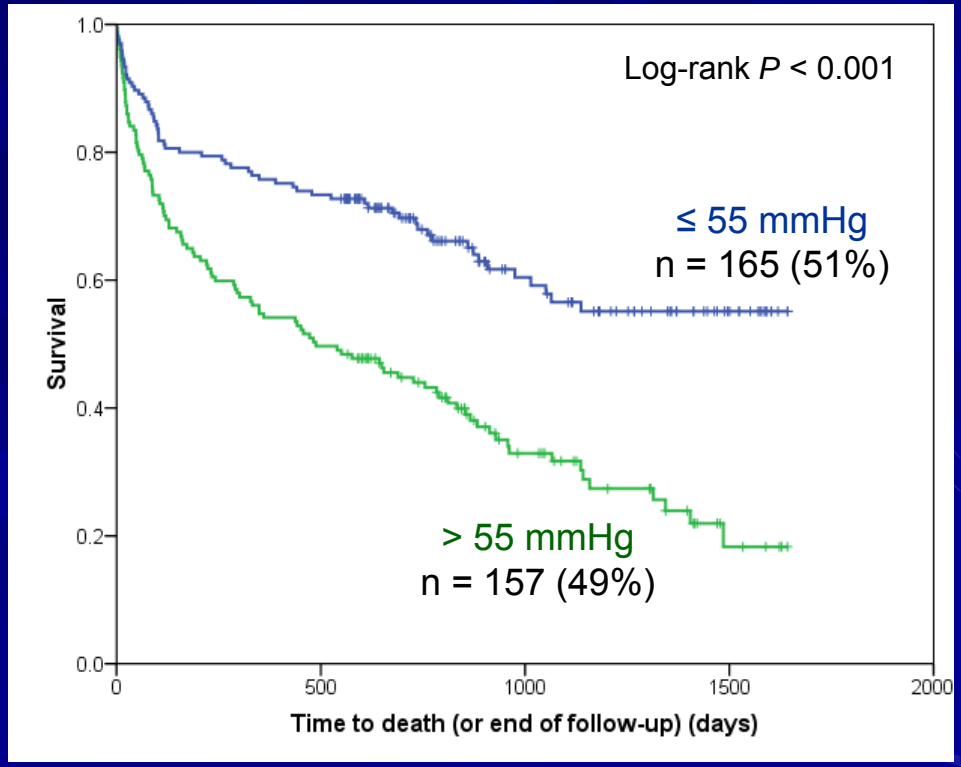
- Atrial arrhythmias, pacemaker
- Rheumatic heart dis., organic TV disease, TV malcoaptation, previous aortic / mitral surgery
- RV / RA enlargement, RA pressure
- LVEF, MR

Survival – by RV Function, PA Pressure

RV dysfunction (≥ moderate)



PA pressure > 55 mmHg (median)



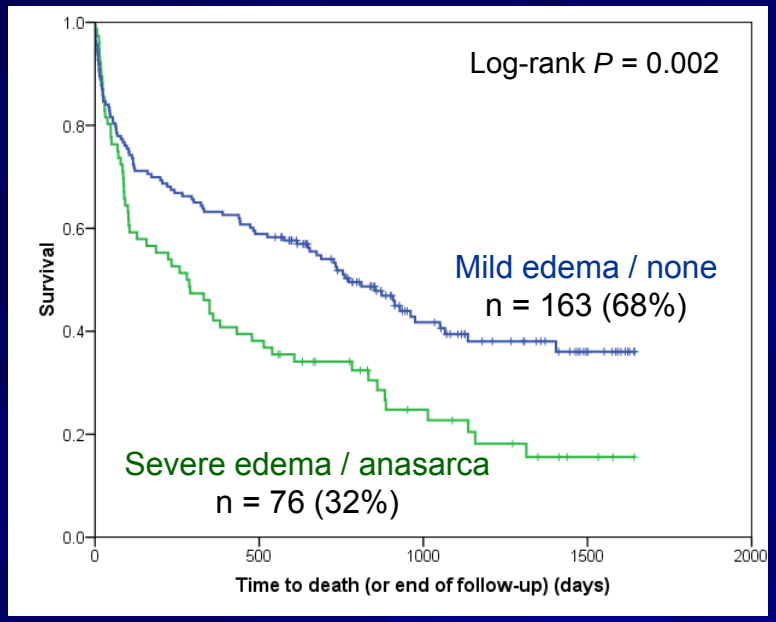
Clinical Predictors of Mortality

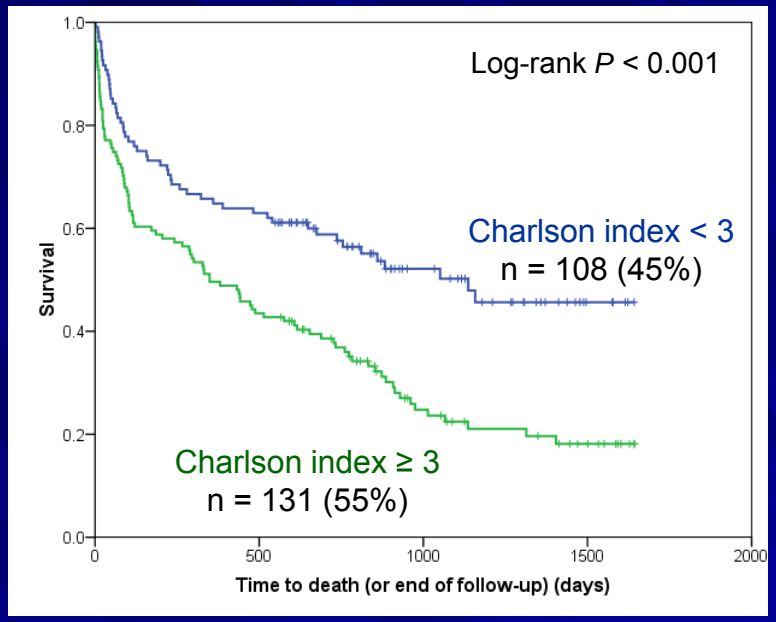
Multivariate Cox Regression* (Hospitalized Pts)

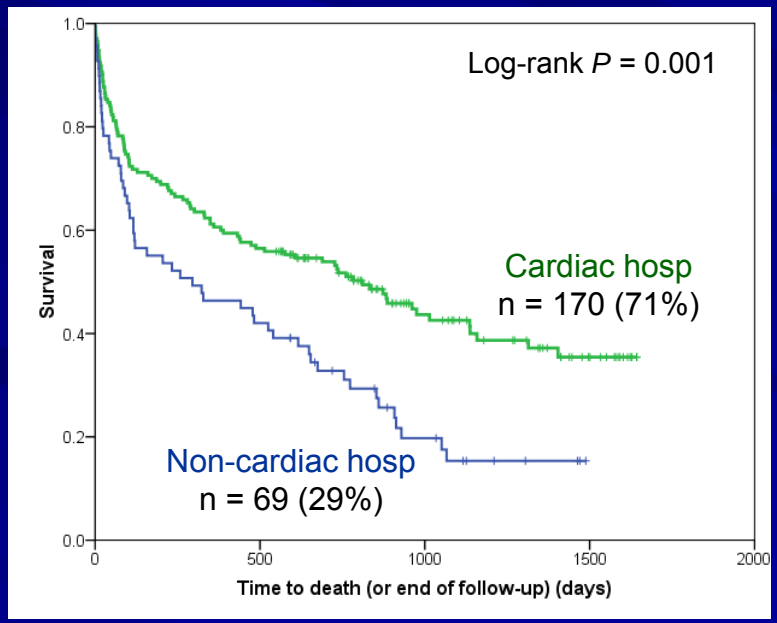
Significant variables	HR	95% CI	*P*
Severe edema / anasarca	2.00	1.36-2.91	<0.001
Furosemide Rx	1.62	1.08-2.43	0.02
Charlson index ≥ 3	1.64	1.08-2.43	0.02
Albumin, per 1 g%	0.63	0.45-0.86	0.004
Cardiac hospitalization	0.56	0.37-0.84	0.005

* Adjusted for age, gender, echocardiographic predictors (RV dysFx, PA pressure)

Survival – by Clinical Parameters







Summary

- Pts with severe TR are typically
  - Elderly
  - High frequency of atrial arrhythmias, pacemakers, pulmonary hypertension
  - Low frequency of rheumatic heart disease, organic TV disease
- Overall mortality ↑↑
- Risk factors for mortality
  - Echocardiographic: RV dysFx, PA pressure ↑↑
  - Clinical: Cardiac (clinical right heart failure, diuretic Rx)
    Non-cardiac morbidity (Charlson index ↑, non-cardiac hosp)

Additional studies are needed to determine whether tricuspid valve surgery may improve survival in pts with severe TR

Study Limitations

- Selection bias (tertiary medical center)
- Retrospective selection of patients

  Retrospective collection of data (echocardiography, clinical data)

  - Prospective follow-up (mortality)
- Clinical data available only for hospitalized pts
  - Echocardiographic data available for all pts
- Some echocardiographic parameters (e.g. RV dysFx) – qualitative
  - Low interobserver variability – qualitative RV Dx[1]
- Analysis of total mortality (cardiac + non-cardiac mortality)
- Limited duration of follow-up (intermediate-term)

Mutlak D et al, *Chest* 2009;135:115-21

Clinical Predictors of Mortality

Univariate-adjusted* Cox Regression (Hospitalized Pts)

Significant variables	HR	95% CI	*P*
Peripheral edema (any degree)	1.31	1.08-1.59	0.006
Severe peripheral edema / anasarca	1.67	1.19-2.35	0.003
Ascites	1.54	1.02-2.33	0.04
Charlson index ≥ 3	1.51	1.05-2.17	0.03
Furosemide Rx	1.43	1.00-2.03	0.05
Albumin, per 1 g%	0.67	0.49-0.90	0.007
Cardiac hospitalization	0.66	0.47-0.93	0.02

* Adjusted for age, gender, echocardiographic predictors (RV dysFx, PA pressure)

Non-significant predictors:

- Hx of MI, ACS (current hospitalization)
- Pulmonary edema (per Hx / current hospitalization)
- Lab: Hb, creatinine, sGOT, GGT

Clinical Predictors of Mortality

Multivariate Cox Regression* (Hospitalized Pts)

	Significant variables	HR	95% CI	*P*
Model A	Severe edema / anasarca	1.66	1.18-2.33	0.004
Clinical – cardiac	Charlson index ≥ 3	1.48	1.04-2.13	0.03
Model B	Severe edema	1.82	1.26-2.64	0.002
Model A	Furosemide Rx	1.70	1.13-2.55	0.01
+ Rx / lab	Albumin, per 1 g%	0.60	0.44-0.82	0.001
Model C	Severe edema	2.00	1.36-2.91	<0.001
Model B	Charlson index ≥ 3	1.64	1.08-2.43	0.02
+ Cardiac hosp. (±)	Furosemide Rx	1.62	1.08-2.43	0.02
	Albumin, per 1 g%	0.63	0.45-0.86	0.004
	Cardiac hospitalization	0.56	0.37-0.84	0.005

* Adjusted for age, gender, echocardiographic predictors (RV dysFx, PA pressure)

Impact of TR on Long-Term Survival (1)

Nath J et al, *JACC* 2004

Table 1. Clinical and Echocardiographic Features of Patients With Tricuspid Regurgitation

	No TR (n = 600)	Mild TR (n = 3,804)	Moderate TR (n = 620)	Severe TR (n = 199)	p Value
Age (yrs)	62.2 ± 12.8	66.0 ± 12.6	71.9 ± 11.7	71.9 ± 12.4	< 0.0001
LVEF (%)	57.3 ± 9.1	55.4 ± 11.6	47.1 ± 15.6	40.4 ± 17.2	< 0.0001
RV dilation	8%	11%	35%	66%	< 0.0001
RV dysfunction	3%	8%	30%	61%	< 0.0001
Dilated IVC	6%	11%	44%	76%	< 0.0001

Data are presented as the mean value ± SD or percentage of patients.
IVC = inferior vena cava; LVEF = left ventricular ejection fraction; RV = right ventricular; TR = tricuspid regurgitation.

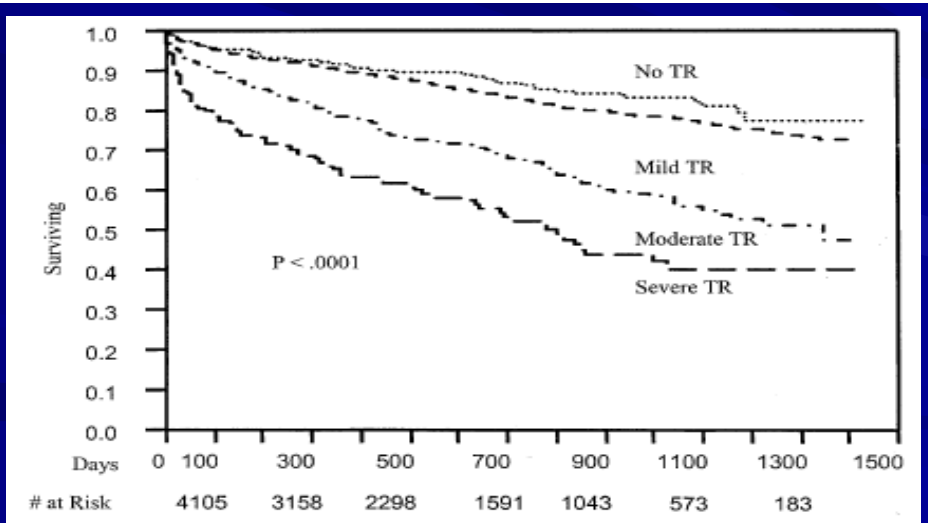


Figure 1. Kaplan-Meier survival curves for all patients with tricuspid regurgitation (TR). Survival is significantly worse in patients with moderate and severe TR.

Impact of TR on Long-Term Survival (2)

Nath J et al, *JACC* 2004

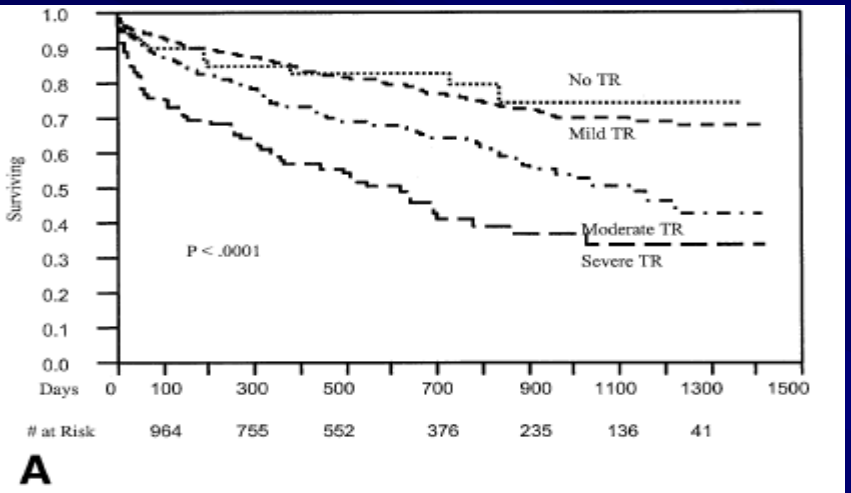


Figure 3. Kaplan-Meier survival curve for **(A)** patients with tricuspid regurgitation (TR) and a low left ventricular ejection fraction (<50%) and **(B)** patients with TR and a normal left ventricular ejection fraction

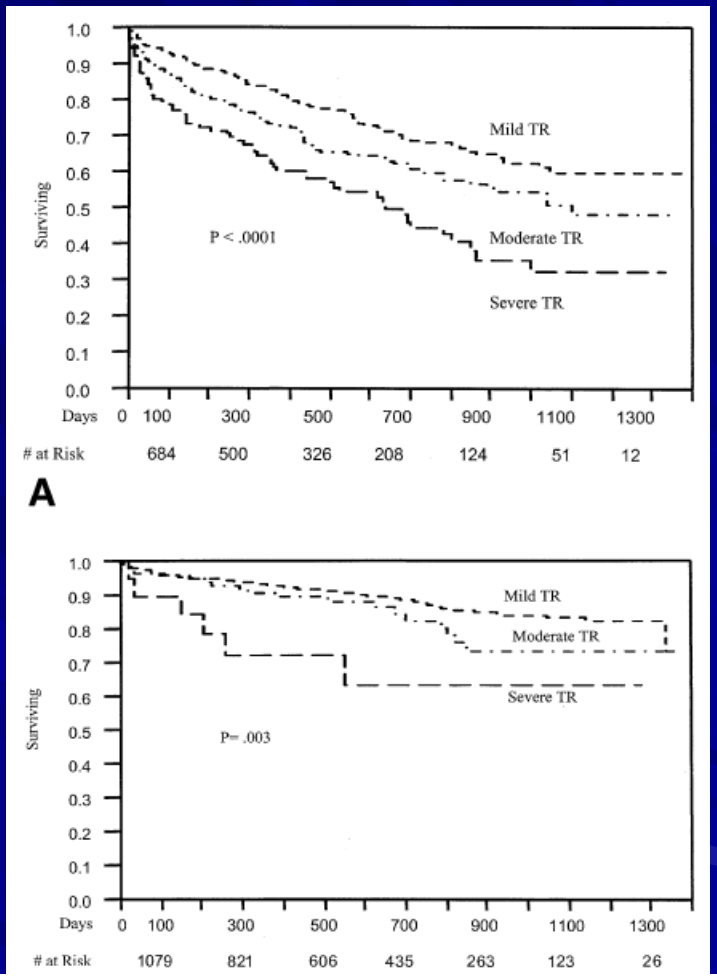
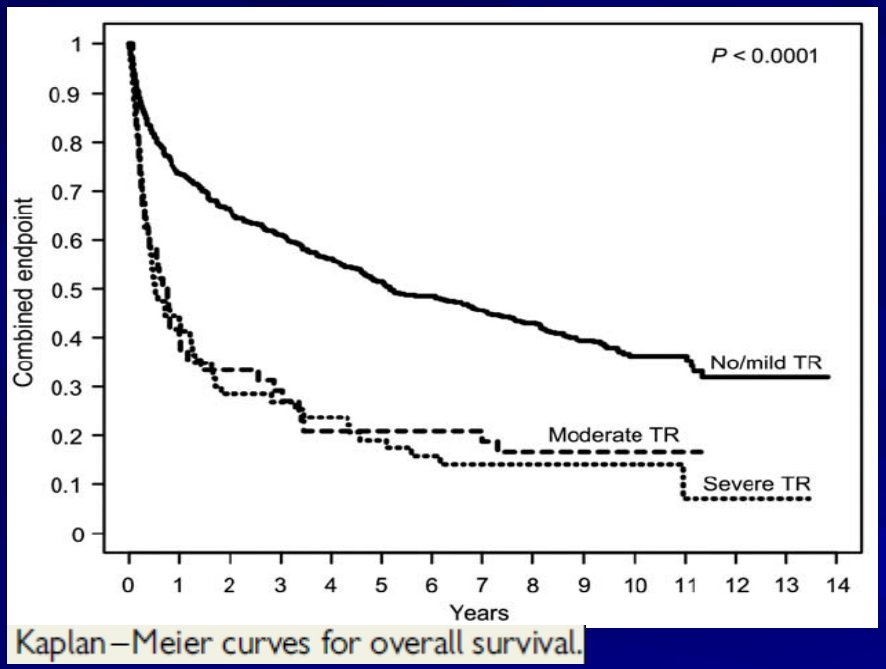


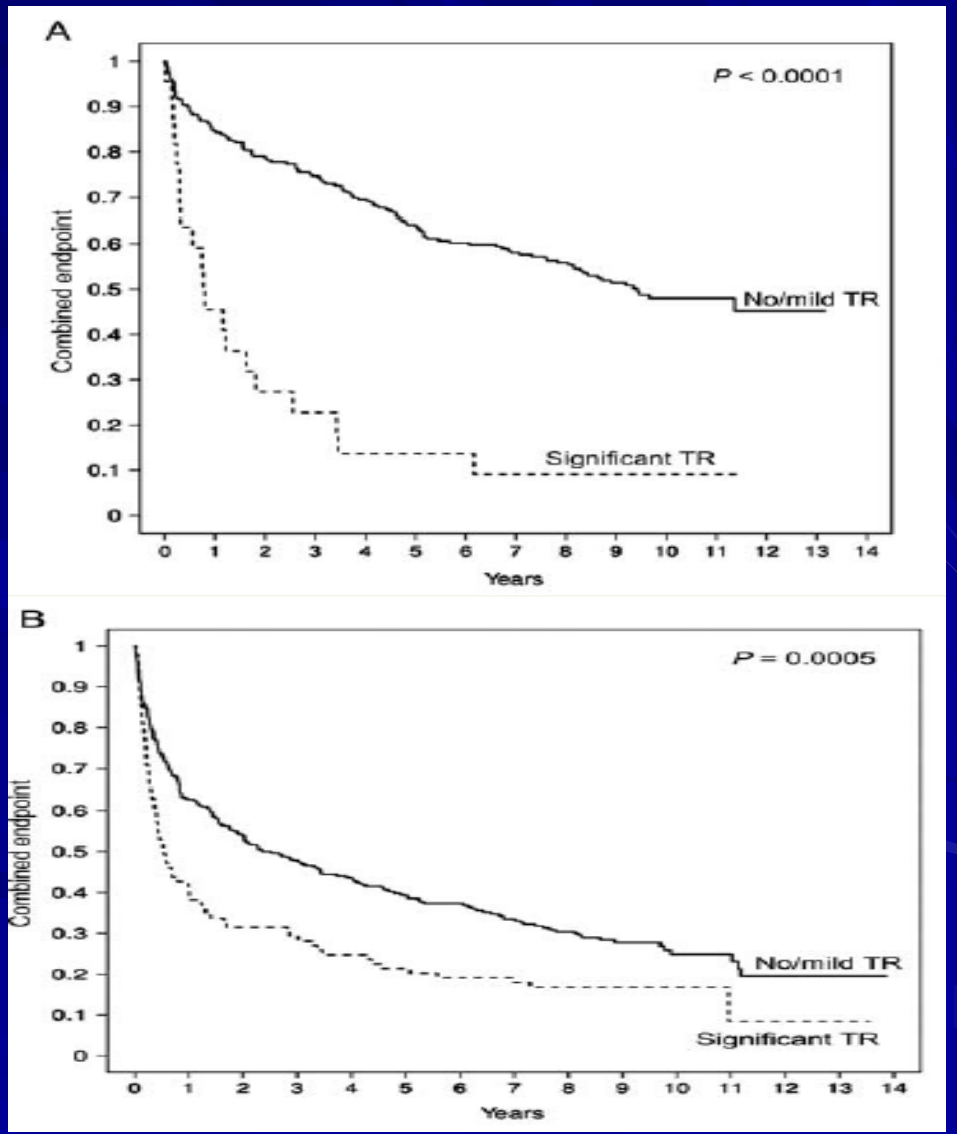
Figure 2. Kaplan-Meier survival curves for **(A)** patients with tricuspid regurgitation (TR) and high pulmonary artery systolic pressure (≥40 mm Hg) and **(B)** patients with TR and normal pulmonary artery systolic pressure (<40 mm Hg).

Impact of TR on Survival in Patients with Chronic Heart Failure

Neuhold S et al, *Eur Heart J* 2013



Kaplan–Meier curves for overall survival.



Impact of Functional Tricuspid Regurgitation on Heart Failure and Death in Patients with Functional Mitral Regurgitation and Left Ventricular Dysfunction (1)

Agricola E et al, *Eur J Heart Failure* 2012

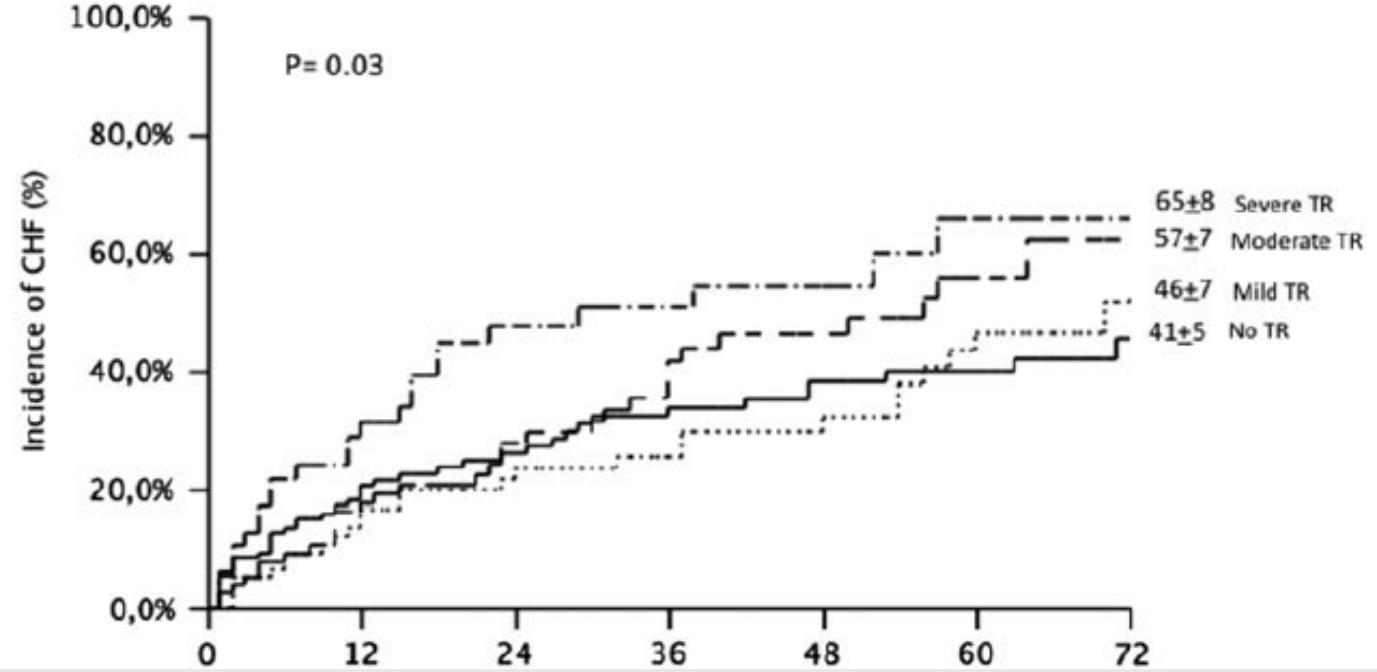


Figure 1 Incidence of congestive heart failure (CHF) in patients with functional mitral regurgitation according to the degree of functional tricuspid regurgitation (TR). The event rates at 6 years are indicated ± the standard error.

Impact of Functional Tricuspid Regurgitation on Heart Failure and Death in Patients with Functional Mitral Regurgitation and Left Ventricular Dysfunction (2)

Agricola E et al, *Eur J Heart Failure* 2012

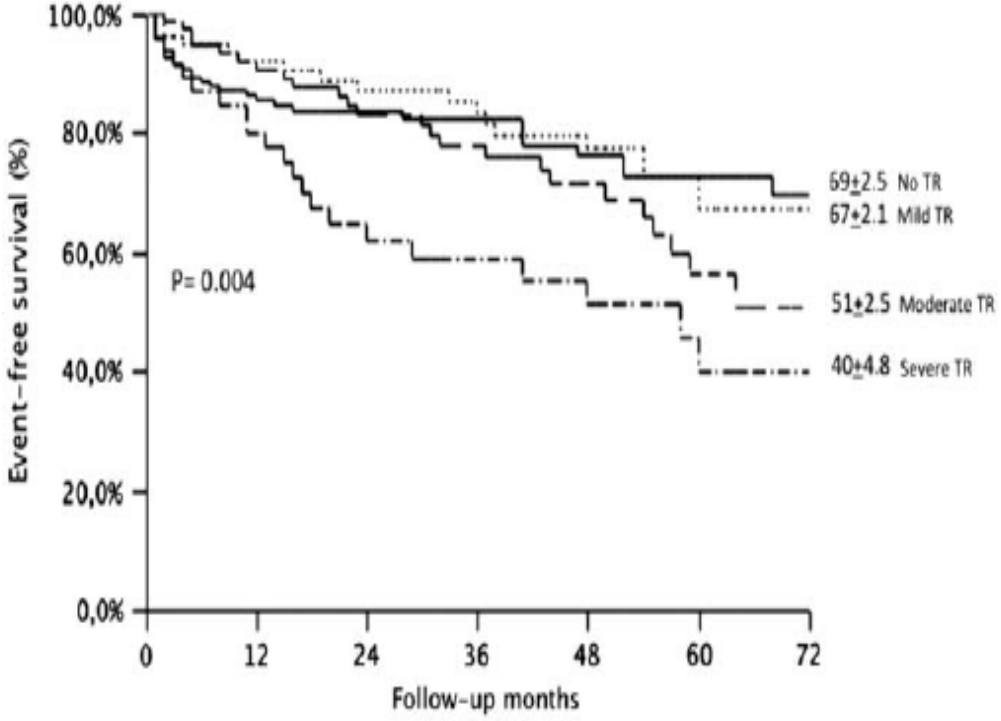


Figure 2 Survival free of all-cause mortality in patients with functional mitral regurgitation according to the degree of functional tricuspid regurgitation (TR). The event rates at 6 years are indicated ± the standard error.

Table 3 Multivariate predictors of all-cause mortality

	HR (95% CI)	*P*-value
Age	0.8 (0.6–1.2)	0.7
EF	1.0 (0.9–1.0)	0.07
PAPs	1.3 (1.0–1.8)	0.03
Moderate to severe MR	1.8 (1.3–2.1)	0.01
Moderate to severe FTR	1.6 (1.2–2.1)	0.01
NYHA class III–IV (%)	2.8 (1.2–8.7)	0.003
Right ventricular dysfunction	2.1 (1.1–4.7)	0.03
Atrial fibrillation (%)	1.6 (1.2–4.5)	0.01
Renal insufficiency (%)	3.1 (1.2–8.0)	0.001

Prognostic Implications of Tricuspid Regurgitation in Patients with Severe Aortic Regurgitation: Results from a Cohort of 756 Patients

Varadarajan P et al, *Interact Cardiovasc Thorac Surg* 2012

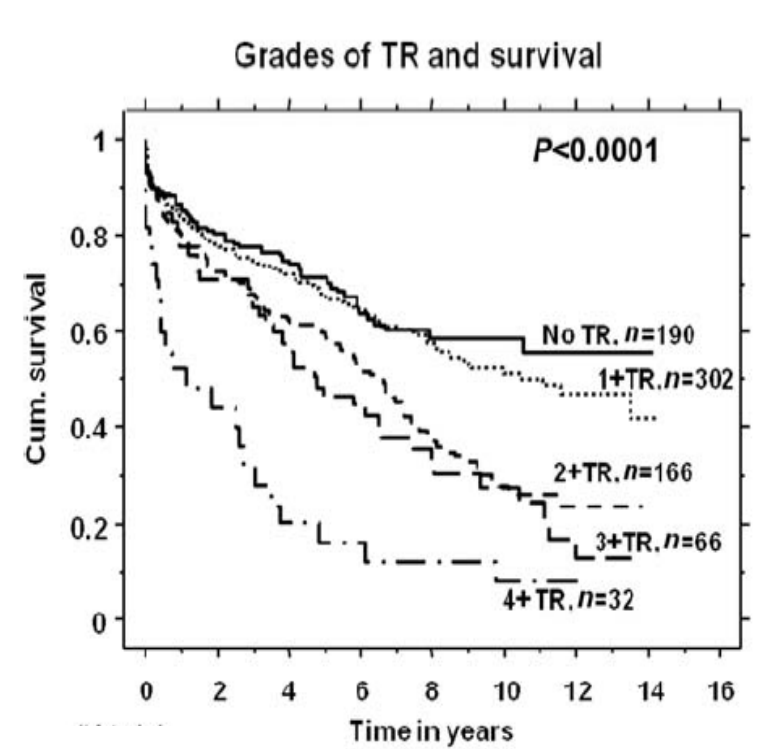
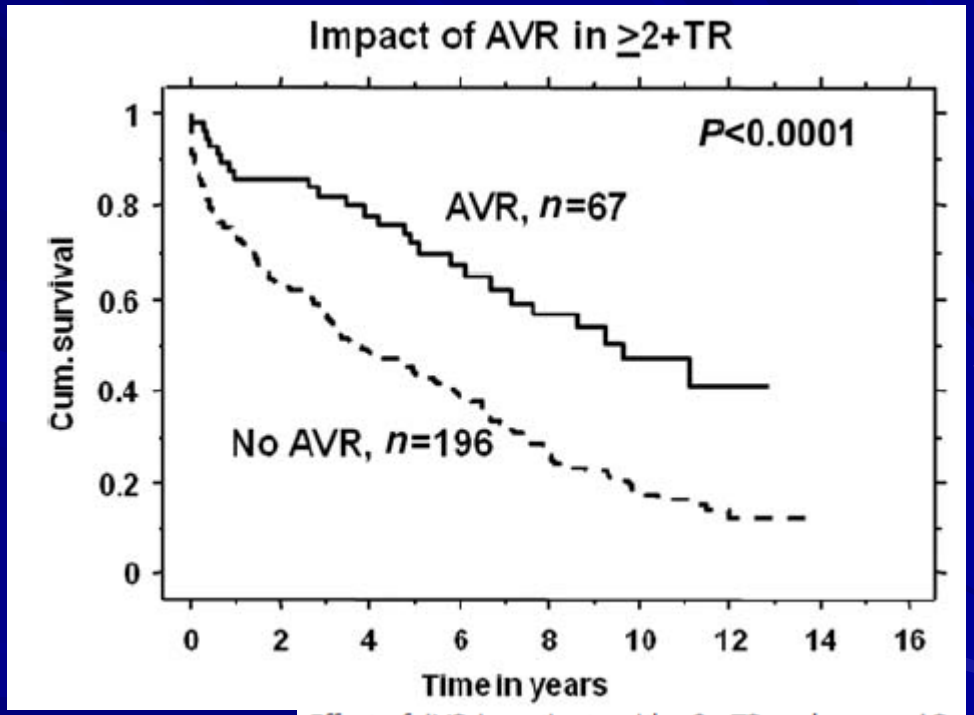


Figure 1: Survival in different grades of TR in patients with severe aortic regurgitation (AR).



Effect of AVR in patients with ≥2+ TR and severe AR.

Charlson comorbidity index

Charlson weights	Conditions	Ghali weights
1[a]	Myocardial infarct	1[a]
1	Congestive heart failure	4
1	Peripheral vascular disease	2
1	Cerebrovascular disease	1
1	Dementia	–
1	Chronic pulmonary disease	–
1	Connective tissue disease	–
1	Ulcer disease	–
1	Mild liver disease	–
1	Diabetes	–
2	Hemiplegia	–
2	Moderate or severe renal disease	3
2	Diabetes with end organ damage	–
2	Any tumour	–
2	Leukaemia	–
2	Lymphoma	–
3	Moderate or severe liver disease	–
6	Metastatic solid tumour	–
6	AIDS	–

[a] Charlson: acute and old myocardial infarct (MI); Ghali: acute MI = 1, old MI = 0.

Non-cardiac causes of hospitalization

- Rheumatology
- Oncology
- Gynecology
- ENT
- Neurosurgery
- Internal medicine departments (pneumonia, skin/UT infection, chronic lung disease exacerbation.…)
- Orthopedics
- Hematology