Supplementary Online Content

Huston JH, Maron BA, French J, et al. Association of mild echocardiographic pulmonary hypertension with mortality and right ventricular function. *JAMA Cardiol*. Published online September 18, 2019. doi:10.1001/jamacardio.2019.3345

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

Supplemental Description of Clinical Data and Comorbidity Phenotyping

The demographic, comorbidity, and laboratory data collected were the values closest to the date of the echocardiogram. Comorbidities were defined based on a combination of International Classification of Diseases-9 (ICD9) coding, previously validated algorithms, and laboratory data as described previously (**Supplemental Table**).[1-9] Clinical heart failure was defined by a combination of 1 more ICD9 codes (425.*, 428.*) with 1 or more elevate BNP (>100) and 1 or more loop diuretic. Heart failure with reduced ejection fraction (HFrEF) was defined as heart failure plus a LV ejection fraction (EF) <50% and heart failure with preserved ejection fraction (HFpEF) as heart failure plus a LVEF ≥50%. Left sided valvular disease was defined as moderate or greater severity of aortic insufficiency, aortic stenosis, and mitral insufficiency or any degree of mitral stenosis. Race was determined by administrative records collected during routine clinical care. Both inpatients and outpatients were included in this study.

Supplemental Description of Echocardiographic Data

We excluded patients with values that were non-physiologic or suggestive of data entry errors based on accepted thresholds for RVSP (<8mmHg or >159mmHg) and TRV (<0.8 or >6.2m/s).[10] Reported echocardiographic data were extracted for left atrial size, left ventricular (LV) end diastolic diameter, LV ejection fraction, and interventricular septal diameter for secondary analyses. Beginning in 2010 left atrial volume index was reported as a standard measure of left atrial size with left atrial diameter used prior to that time. LV diastolic dysfunction was reported by grade (e.g. 1-3) as interpreted by the expert interpreter and indicated in the clinical report. RV size and function were assessed both qualitatively (i.e. normal, mild, moderate, severe)[11] and quantitatively by RV end diastolic diameter and the tricuspid annular plane systolic excursion (TAPSE).[12] Qualitative RV function was as interpreted by expert

readers in clinical practice incorporating qualitative measures and visual recognition.[13,14] Our echocardiography laboratory did not routinely report quantitative measures of RV function measures prior to 2009. Starting in 2009, the most routinely collected metric of RV function was the tricuspid annular plane systolic excursion (TAPSE).

Supplemental Description of Outcomes

If no death was recorded in the Social Security Death Index at the time our analysis was conducted (February 1, 2017) these patients were considered to be alive. Survivors were censored using the date of their last contact with Vanderbilt's medical system (i.e. clinic visit, discharge, prescription fill, etc.) as previously described.[6,8,9,15] This censoring method is conservative because it assumes the no subjects have died between the last contact with Vanderbilt.

Supplemental Description of Statistical Analysis

Time cohorts were defined by 3 to 5-year increments: 1997-1999, 2000-2004, 2005-2009, and 2010-2014 to adjust for any effect of time period of clinical care. We elected to adjust for a clinical diagnosis of heart failure as opposed to by LVEF because normal LVEF values do not capture risk related to HFpEF. Left atrial dilation was defined as a left atrial anterior-posterior diameter greater than 4cm.[16,17] We examined the association between mortality and mild echocardiographic PH (ePH) among a subgroup of patients with established PH risk factors (heart failure, COPD, obstructive sleep apnea, and systemic sclerosis). Associations with race and sex were also examined. We also examined potential interactions between RVSP or TRV and sex and race in Cox regression models. We analyzed RVSP and TRV separately given the subjectivity in estimating RAP to calculate RVSP.

Supplemental Table. Comorbidity identifiers

Comorbidity	ICD-9 Code	Other Variables
Heart Failure	425.*, 428.*	AND 1 or more BNP>100 AND 1 or more loop diuretic (furosemide, bumetanide, torsemide, ethacrynic acid or metolazone)
Hypertension	401.* – 405.*	1 or more Problem List: "hypertension", "htn" AND 0 in the Problem List: "portal hypertension", "pulmonary hypertension", "rv hypertension", "intracranial hypertension", "phtn"
Chronic Obstructive Pulmonary Disease	2 or more 491.*, 492.*, 496	AND 1 or more meds: "roflumilast", "daliresp", "tiotropium", "spiriva", "ipratropium", "atrovent", "theophylline", "slo-bid", "slo-phyllin", "theo-dur", "theo 24", "theo24", "theo-24", "uniphyl", "salmeterol", "serevent", "formoterol", "foradil", "albuterol + ipratropium", "albuterol / ipratropium", "ipratropium bromide / albuterol sulfate", "ipratropium bromide with albuterol sulfate", "combivent", "duoneb", "albuterol", "proventil", "proair", "ventolin", "fluticasone", "salmeterol", "advair", "budesonide/formoterol", "budesonide / formoterol", "budesonide - formoterol", "budesonide-formoterol", "mometasone/formoterol", "mometasone / formoterol", "dulera", "beclomethaosne", "qvar", "budesonide", "pulmicort", "fluticasone", "flovent", "mometasone", "asmanex"
Interstitial Lung Disease	515, 516.3*, 516.4, 516.5	
Coronary Artery Disease	410.*-414.*, V45.82	OR CPT codes: 33534-33536, 33510-33523, 92980-92982, 92984, 92995-92996
Atrial Fibrillation	427.3*	4 or more of the following: "afib","a fib","atrial-fib","atrial fib","a flutter","atrial flutter","atrial-flutter" in the Problem List or clinical documents (non-negated, non-family)
Sleep Apnea	327.20-327.23 780.51, 780.53, 780.57	
Diabetes Mellitus	250.*	AND “diabetes” or “dm” in the problem list
Connective Tissue Disease	710.0-710.1, 517.2, 695.4	
Systemic Lupus Erythematosus	710.0, 695.4	
Systemic Sclerosis	710.1*, 517.2*	
Left Sided Valve Disease		1 or more echo with moderate or greater: Aortic stenosis, Aortic Insufficiency, Mitral Regurgitation or any Mitral Stenosis

ICD, International Classification of Diseases-9; CPT, Current Procedures Terminology; BNP, brain natriuretic peptide.

eTable 1. Most frequent indications for echocardiography

Indication	Count (%)
Coronary Artery Disease or Myocardial Infarction	3337 (13)
Dyspnea	3346 (13)
Arrhythmia	3046 (12)
Heart Failure, unspecified	2535 (10)
Aortic Regurgitation or Stenosis	1920 (7)
Murmur, unspecified	1205 (5)
Mitral Regurgitation or Stenosis	1010 (4)
Hypertension	974 (4)
Syncope or Dizziness	955 (4)
Screening for Cardiovascular Disease	948 (4)

eTable 2. Demographic, echocardiographic, and laboratory differences between patients with normal, mild ePH, and ePH by TRV

Variable	TRV (m/sec)		
	≤2.5 (n=25891)	2.6-2.9 (n=10583)	≥3 (n=11070)
Deceased (%)	1127 (4)	836 (8) [a]	1517 (14)
Age, Mean ± SD	55 ±18	63 ± 16 [a]	66 ± 16
Gender			
Male (%)	11270 (44)	4713 (45)	4920 (44)
Female (%)	14612 (56)	5869 (55)	6147 (56)
Race [a]			
Caucasian	20398 (84)	8412 (85)	8403 (81)
Black	2986 (12)	1282 (13)	1753 (17)
Other	849 (4)	260 (3)	210 (3)
BMI, kg/m^2	28.6 ±7	29.2 ±7.5 [a]	28.8 ±7.9
RVSP, mmHg	26 ±5	36 ± 4 [a]	55 ± 16
TRV, m/sec	2.2 ± 0.3	2.7 ±0.1 [a]	3.4 ± 0.5
Comorbidities			
Hypertension	17620 (69)	8187 (78) [a]	8644 (80)
COPD	2699 (10)	1674 (16) [a]	2399 (22)
CAD	9185 (35)	4896 (46) [a]	5733 (52)
Atrial Fibrillation	5771 (22)	3377 (32) [a]	4382 (40)
Sleep Apnea	3101 (12)	1366 (13) [a]	1384 (13)
Heart Failure	3614 (14)	2599 (25) [a]	4125 (37)
LVEF <40% [a]	1003 (29)	792 (31)	1278 (32)
LVEF 40-50%	497 (14)	404 (16)	570 (14)
LVEF >50%	2000 (57)	1319 (52)	2116 (53)
HFrEF	1370 (5)	1084 (10)[a]	1705 (16)
HFpEF	522 (2)	337 (3) [a]	561 (5)
Left Sided Valvular Disease	2196 (9)	1631(16) [a]	2896 (28)
Diabetes Mellitus	8250 (32)	3905 (37) [a]	4424 (40)
Systemic Sclerosis	152 (1)	90 (1) [a]	200 (2)
Echocardiographic Parameters			
LVEF, %	55 ± 9	53 ± 12 [a]	50 ± 15
Mitral Inflow E/a Ratio	1.2 ± 0.7	1.2 ±0.6	1.4 ± 0.8
Left Atrial Diameter, mm	37 ± 7	40 ± 8 [a]	43 ± 9
Left Atrial Volume Index, mL/m^2	25 ± 10	33 ± 21 [a]	39 ± 16
Interventricular Septal Diameter, mm	12 ± 8	13 ± 8 [a]	13 ± 8
Left Ventricular Posterior Wall Diameter, mm	10 ± 2	10 ± 2 [a]	11 ± 2
RV End Diastolic Diameter, cm	2.9 ± 0.8	3.0 ± 0.6 [a]	3.2 ± 0.7
TAPSE, cm	2.1 ± 0.5	2.1 ± 0.6 [a]	1.8 ± 0.6
Diastolic Dysfunction [a] (n=8728)			

Variable	TRV (m/sec)		
	≤2.5 (n=25891)	2.6-2.9 (n=10583)	≥3 (n=11070)
Grade 1	3863 (86)	1474 (72)	1107 (52)
Grade 2	532 (12)	407 (20)	574 (27)
Grade 3	101 (2)	156 (8)	446 (21)
RV size, qualitative [a] (n=26848)			
Normal	14221 (94)	5424 (90)	4171 (75)
Mildly Dilated	731 (5)	481 (8)	896 (16)
Moderately Dilated	137 (1)	110 (2)	386 (7)
Severely Dilated	21 (<1)	17 (<1)	117 (2)
RV function, qualitative[a] (n= 26538)			
Normal	14386 (96)	5499 (93)	4380 (80)
Mildly reduced	337 (2)	244 (4)	553 (10)
Moderately reduced	196 (1)	149 (3)	407 (7)
Severely reduced	46 (<1)	47 (1)	160 (3)
Laboratory Values			
BNP, pg/mL (n=15082)	148 (51-435)	240 (85-635)	374 (150-919)
Creatinine, mg/dL (n=40846)	1.1 ± 1.1	1.3 ± 1.3 [a]	1.5 ± 1.6
CRP, mg/L (n=10352)	8.6 (2-55)	17 (3.4-88)[a]	21 (5-99)
eGFR, mL/min/1.73L^2 (n=40784)	83 ± 39	75 ± 37 [a]	68 ± 39
Hemoglobin A1c, % (n=18148)	6.2 ± 1.5	6.3 ± 1.4 [a]	6.4 ± 1.5
HDL, mg/dL (n=24542)	50 ± 18	48 ± 18 [a]	45 ± 18
LDL, mg/dL (n=23988)	100 ± 37	96 ± 39 [a]	90 ± 38
Triglycerides, mg/dL= (n=25366)	144 ± 124	145 ± 112	143 ± 114
Hemoglobin, g/dL (n=40002)	12.7 ± 2	12.1 ± 2 [a]	11.7 ± 2
Medications			
Beta Blocker	15811 (61)	7533 (71) [a]	7982 (72)
ACE Inhibitor	12390 (48)	5997 (57) [a]	6491 (59)
Calcium Channel Blocker	11708 (45)	5715 (54) [a]	6076 (55)
ARB	6868 (27)	3192 (30) [a]	3131 (28)
Loop Diuretic	9718 (38)	4616 (44) [a]	4851 (44)
Non-Loop Diuretic	12042 (47)	6544 (62) [a]	8206 (74)

Variable	TRV (m/sec)		
	≤2.5 (n=25891)	2.6-2.9 (n=10583)	≥3 (n=11070)
Mineralocorticoid Antagonist	3735 (14)	2082 (20) [a]	2769 (25)
Alpha Blocker	1225 (5)	641 (6) [a]	661 (6)
Alpha-2 Agonist	3552 (14)	1782 (17) [a]	1967 (18)
Nitrates	8048 (31)	4034 (38) [a]	4781 (43)
Statins	13215 (51)	6180 (58) [a]	5999 (54)
Nicotinic Acid	1209 (5)	531 (5) [a]	430 (4)
Fibrates	5594 (22)	2804 (26) [a]	2870 (26)
Oral Anticoagulant	7153 (28)	3799 (36) [a]	4947 (45)
Subcutaneous Anticoagulant	5722 (22)	2907 (27) [a]	3344 (30)
Any PAH Medication	11591 (45)	5659 (53) [a]	6311 (57)
PAH CCB	11232 (43)	5504 (52) [a]	5863 (53)
Prostacyclin	372 (1)	246 (2) [a]	775 (7)
Endothelin Receptor Blocker	48 (0)	35 (0) [a]	327 (3)
Phosphodiesterase-5 Inhibitor	730 (3)	348 (3)	701 (6)
Guanylate Cyclase Stimulator	1 (0)	0 (0)	5 (0)
Metformin	4072 (16)	1805 (17) [a]	1707 (15)
Insulin	8748 (34)	4562 (43) [a]	5270 (48)
Sulfonylurea	2499 (10)	1287 (12) [a]	1459 (13)
Thiazolidinedione	1033 (4)	577 (5) [a]	630 (6)

Continuous variables are presented as mean ± standard deviation with the exception of BNP and CRP which are presented as median (25^{th}- 75^{th} percentile). [a] $p<0.05$ comparing TRV of ≤2.6 versus 2.6-2.9m/sec. BMI, body mass index; RVSP, right ventricular systolic pressure; TRV, tricuspid regurgitant velocity; COPD, chronic obstruction pulmonary disease; CAD, coronary artery disease; EF, ejection fraction; HFrEF, Heart Failure with reduced ejection fraction; HFpEF: Heart Failure with preserved ejection fraction; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein, ACE, angiotensin converting enzyme; CCB, calcium channel blocker; ARB, Angiotensin receptor blocker; PAH, pulmonary arterial hypertension.

eTable 3. Adjusted risk of mortality according to RVSP and TRV extracted from Figure 4A and eFigure 3A in the Supplement

RVSP (mmHg)	Hazard Ratio (CI)	TRV (m/sec)	Hazard Ratio (CI)
25	1.23 (0.98- 1.54)	2.4	1.25 (1.12- 1.40)
30	1.53 (1.16- 2.01)	2.6	1.62 (1.44- 1.83)
35	2.08 (1.59- 2.72)	2.8	2.08 (1.83- 2.37)
40	2.71 (2.09- 3.51)	3	2.51 (2.19- 2.88)
45	3.28 (2.54- 4.23)	3.2	2.88 (2.50- 3.31)
50	3.74 (2.91- 4.82)	3.4	3.18 (2.77- 3.66)
55	4.10 (3.18-5.28)	3.6	3.46 (3.01- 3.98)
60	4.37 (3.39- 5.63)	3.8	3.74 (3.24- 4.32)

The reference values were a RVSP of 15mmHg and TRV of 1.9m/sec. RVSP, right ventricular systolic pressure; TRV, tricuspid regurgitant velocity; CI, confidence interval. Adjusted for the following potential confounders *a priori* based on clinical knowledge: age, race, sex, body mass index, hypertension, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, left sided valve disease, left atrial dilation, interstitial lung disease, chronic obstructive pulmonary disease, connective tissue disease, coronary disease, atrial fibrillation, sleep apnea, diabetes and by cohorts of time in which echo was performed

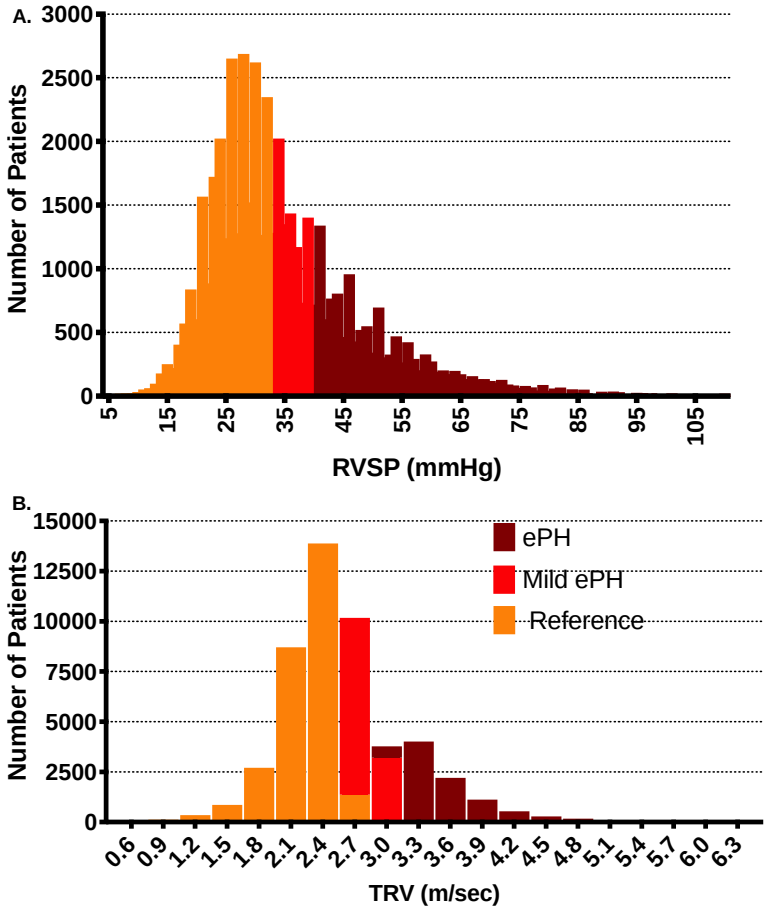
eTable 4. Adjusted risk of mortality according to RVSP and TRV stratified by sex extracted from Figure 4B and eFigure 3B in the Supplement

RVSP (mmHg)	Hazard Ratio (CI)		TRV (m/sec)	Hazard Ratio (CI)	
	Male	Female		Male	Female
25	1.16 (0.92- 1.46)	1.29 (1.03- 1.62)	2.4	1.19 (1.06- 1.34)	1.35 (1.20- 1.52)
30	1.41 (1.07- 1.86)	1.66 (1.25- 2.19)	2.6	1.52 (1.34- 1.71)	1.81 (1.58- 2.06)
35	1.89 (1.44-2.47)	2.34 (1.78- 3.07)	2.8	1.91 (1.66- 2.18)	2.39 (2.06- 2.77)
40	2.41 (1.85- 3.13)	3.15 (2.41- 4.11)	3	2.24 (1.93- 2.60)	2.95 (2.51- 3.47)
45	2.84 (2.19- 3.69)	3.92 (3.00- 5.12)	3.2	2.49 (2.13- 2.92)	3.45 (2.91- 4.09)
50	3.15 (2.42- 4.10)	4.58 (3.50- 5.99)	3.4	2.68 (2.27- 3.15)	3.90 (3.27- 4.64)
55	3.33 (2.55- 4.36)	5.11 (3.90- 6.72)	3.6	2.82 (2.37- 3.35)	4.31 (3.60- 5.17)
60	3.43 (2.61- 4.53)	5.56 (4.22- 7.33)	3.8	2.95 (2.45- 3.56)	4.75 (3.93- 5.75)

The reference values were a RVSP of 15mmHg and TRV of 1.9m/sec. RVSP, right ventricular systolic pressure; TRV, tricuspid regurgitant velocity; CI, confidence interval. Adjusted for the following potential confounders *a priori* based on clinical knowledge: age, race, sex, body mass index, hypertension, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, left sided valve disease, left atrial dilation, interstitial lung disease, chronic obstructive pulmonary disease, connective tissue disease, coronary disease, atrial fibrillation, sleep apnea, diabetes and by cohorts of time in which echo was performed

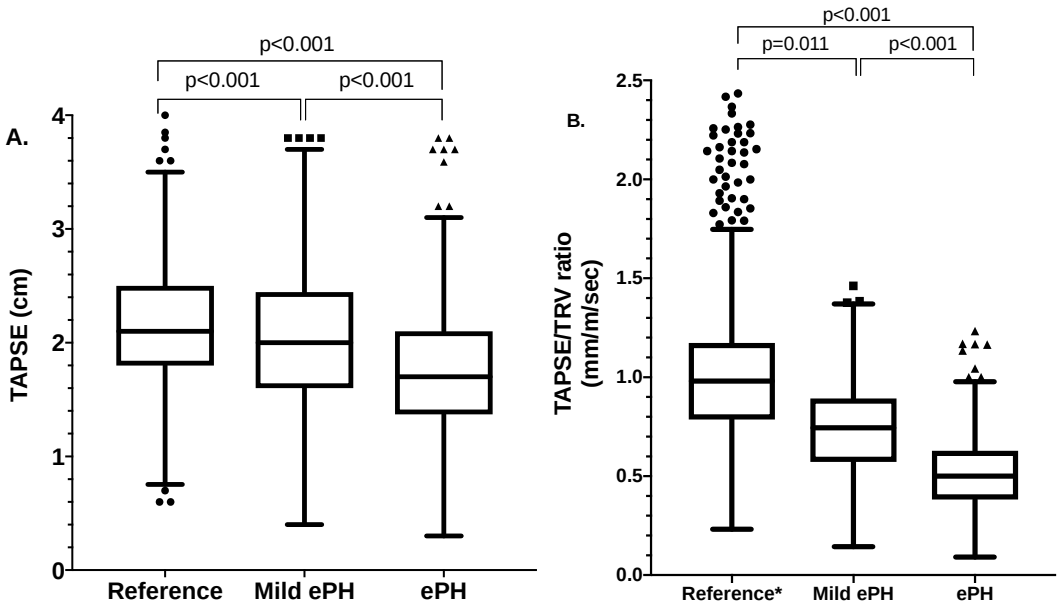
eFigure 1. Frequency distribution of RVSP and TRV values reported

RVSP and TRV values in the Mild ePH range are frequent. RVSP, right ventricular systolic pressure; TRV, tricuspid regurgitant velocity; PH, pulmonary hypertension.



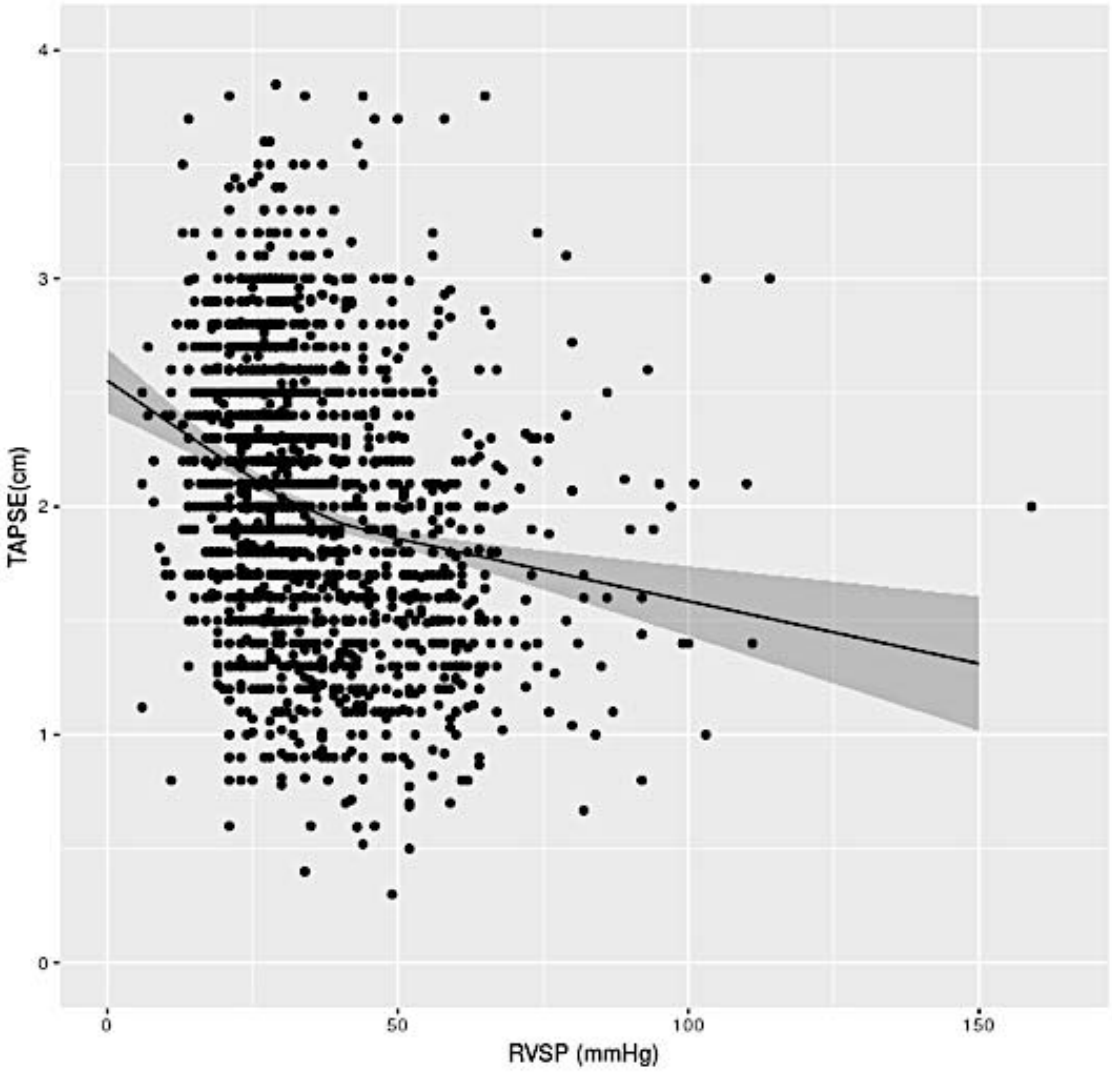
eFigure 2. Whisker plots of RV function by TAPSE and RV-PA coupling by TAPSE/RVSP ratio stratified by degree of PH by TRV

A. RV Function by TAPSE is significantly lower in patients with Mild ePH and ePH as compared with the reference. **B.** RV-PA coupling by TAPSE/TRV worsens with increasing degrees of ePH. *Four values are outside the range in the reference group and are not included TRV, tricuspid regurgitant velocity; RV, right ventricular; PA, pulmonary arterial; TAPSE, tricuspid annular systolic excursion; ePH, echocardiographic pulmonary hypertension.



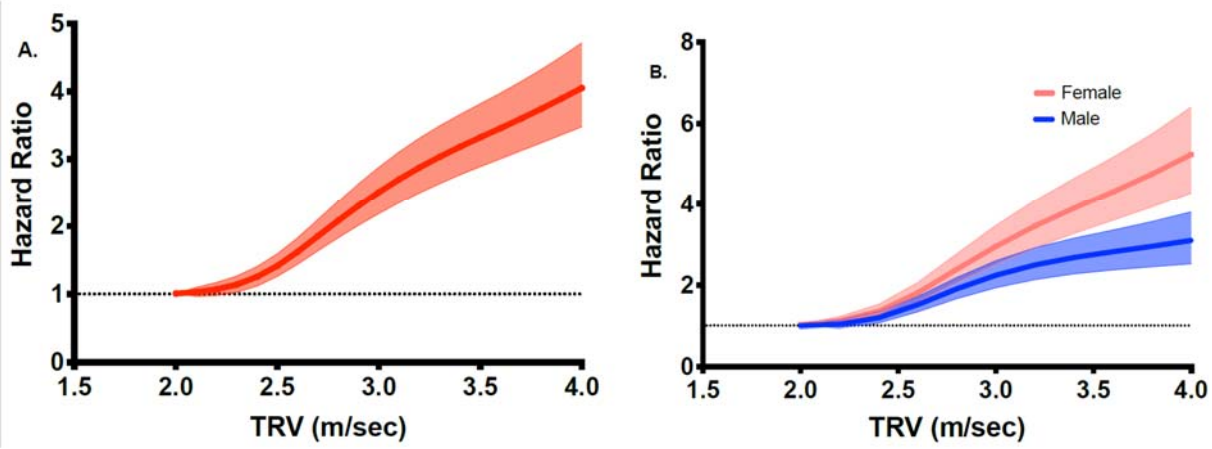
eFigure 3. Relationship between TAPSE and RVSP

There was a significant non-linear, inverse relationship between TAPSE and RVSP ($p<0.01$).



eFigure 4. Adjusted risk of Mortality by TRV and stratified by sex

A. Mortality increased significantly as TRV increased. **B.** Women had a higher risk of mortality compared to men at a given TRV (p for interaction <0.001). Reference value was a TRV of 1.9m/sec. See eTables 2 and 3 for Hazard Ratios. TRV, tricuspid regurgitant velocity. Adjusted for the following potential confounders *a priori* based on clinical knowledge: age, race, sex, body mass index, hypertension, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, left sided valve disease, left atrial dilation, interstitial lung disease, chronic obstructive pulmonary disease, connective tissue disease, coronary disease, atrial fibrillation, sleep apnea, diabetes and by cohorts of time in which echo was performed



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