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ORIGINAL RESEARCH

Right Ventricular Pulmonary Artery Coupling and Mortality in Cardiac Intensive Care Unit Patients

Jacob C. Jentzer, MD; Nandan S. Anavekar, MBBCh; Yogesh N. V. Reddy, MBBS; Dennis H. Murphree, PhD; Brandon M. Wiley, MD; Jae K. Oh, MD; Barry A. Borlaug, MD

BACKGROUND: Impaired right ventricular (RV) pulmonary artery coupling has been associated with higher mortality in patients with chronic heart disease, but few studies have examined this metric in critically ill patients. We sought to evaluate the association between RV pulmonary artery coupling, defined by the ratio of tricuspid annular peak systolic tissue Doppler velocity (TASV)/estimated RV systolic pressure (RVSP), and mortality in cardiac intensive care unit patients.

METHODS AND RESULTS: Using a database of unique cardiac intensive care unit admissions from 2007 to 2018, we included patients with TASV/RVSP ratio measured within 1 day of hospitalization. Hospital mortality was analyzed using multivariable logistic regression, and 1-year mortality was analyzed using multivariable Cox proportional-hazards analysis. We included 4259 patients with a mean age of 69±15 years (40.1% women). Admission diagnoses included acute coronary syndrome in 56%, heart failure in 52%, respiratory failure in 24%, and cardiogenic shock in 12%. The mean TASV/RVSP ratio was 0.31±0.14, and in-hospital mortality occurred in 7% of patients. Higher TASV/RVSP ratio was associated with lower in-hospital mortality (adjusted unit odds ratio, 0.68 per each 0.1-unit higher ratio; 95% CI, 0.58–0.79; $P<0.001$) and lower 1-year mortality among hospital survivors (adjusted unit hazard ratio, 0.83 per each 0.1-unit higher ratio; 95% CI, 0.77–0.90; $P<0.001$). Stepwise decreases in hospital and 1-year mortality were observed in each higher TASV/RVSP quintile. The TASV/RVSP ratio remained associated with mortality after adjusting for left ventricular systolic and diastolic function.

CONCLUSIONS: A low TASV/RVSP ratio is associated with increased short-term and long-term mortality among cardiac intensive care unit patients, emphasizing importance of impaired RV pulmonary artery coupling as a determinant of poor prognosis. Further study is required to determine whether interventions to optimize RV pulmonary artery coupling can improve outcomes.

Key Words: cardiac intensive care unit ■ Doppler ■ echocardiography ■ mortality ■ pulmonary hypertension ■ right heart failure ■ right ventricle

Right ventricular (RV) dysfunction causing RV failure is common among hospitalized patients.[1–3] RV dysfunction and RV failure among critically ill patients are typically the results of pulmonary hypertension (PH), RV insults, or both, and these conditions have frequently been associated with adverse outcomes.[3–8] RV function can be assessed using measures of longitudinal RV motion, such as the tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic tissue Doppler velocity (TASV), the former potentially being more load dependent.[3,9] Elevated pulmonary artery (PA) pressures, measured by Doppler echocardiography based on the tricuspid regurgitation (TR) velocity, in the absence of pulmonary valve stenosis, can identify PH, which has been associated with adverse outcomes in critically ill patients.[10,11]

The ability of the RV to compensate with preserved systolic function in the face of an increasing

Correspondence to: Jacob C. Jentzer, MD, Department of Cardiovascular Medicine and Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, The Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: jentzer.jacob@mayo.edu

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study examining the tricuspid annular systolic velocity/right ventricular (RV) systolic pressure ratio, a Doppler-based echocardiographic measure of RV pulmonary artery coupling, for mortality risk stratification in cardiac intensive care unit patients, demonstrating an inverse association with mortality.
- Among the 4259 unique patients, those with higher values of the tricuspid annular systolic velocity/RV systolic pressure ratio were at lower risk of mortality both in hospital (adjusted odds ratio, 0.7 per each 0.1-unit higher) and at 1 year after admission among hospital survivors (adjusted hazard ratio, 0.8 per each 0.1-unit higher).

What Are the Clinical Implications?

- The tricuspid annular systolic velocity and RV systolic pressure should be routinely measured by echocardiography, and their ratio should be calculated for cardiac intensive care unit patients, to identify those patients with impaired RV pulmonary artery coupling hemodynamics who are at elevated risk of adverse outcomes.
- Future studies should elaborate how to incorporate this augmented risk stratification information into clinical practice and evaluate whether treatments targeting improvement in the tricuspid annular systolic velocity/RV systolic pressure ratio, potentially by lowering right atrial or pulmonary artery pressures, can improve clinical outcomes in this patient population.

Nonstandard Abbreviations and Acronyms

CICU	cardiac intensive care unit
PH	pulmonary hypertension
RAP	right atrial pressure
RVSP	right ventricular systolic pressure
TAPSE	tricuspid annular plane systolic excursion
TASV	tricuspid annular peak systolic tissue Doppler velocity
TR	tricuspid regurgitation
TTE	transthoracic echocardiography

afterload is referred to as maintaining RV-PA coupling.[12] Echocardiographic measures of RV-PA coupling involve the ratio of RV longitudinal motion (ie, TAPSE or TASV)/the RV systolic pressure (RVSP) or PA systolic pressure.[3,12] Studies evaluating the TAPSE/RVSP ratio in patients with cardiovascular disease have shown associations between lower TAPSE/RVSP ratio (reflecting worse RV-PA coupling) and adverse outcomes.[12–19] Prior studies evaluating RV-PA coupling using the TASV/RVSP ratio have involved invasive measurements of PA systolic pressure, rather than noninvasive RVSP derived from Doppler transthoracic echocardiography (TTE).[20–24] To our knowledge, no published studies have examined the association between noninvasive measures of RV-PA coupling and outcomes using either the TAPSE/RVSP or TASV/RVSP ratio by TTE in critically ill patients. Because the TASV is potentially less load dependent than TAPSE, we sought to determine the association between RV-PA coupling, as determined by the TASV/RVSP ratio using Doppler TTE, and mortality in unselected cardiac intensive care unit (CICU) patients.

METHODS

Study Population

The authors declare that all supporting data are available within the article and its online supplementary files. This study was approved by the Institutional Review Board of Mayo Clinic (No. 16-000722) as posing minimal risk to patients, and was performed under a waiver of informed consent. We retrospectively analyzed a previously constructed database of consecutive unique adult patients, aged ≥18 years, admitted to the CICU at Mayo Clinic Hospital St. Mary's Campus between January 1, 2007, and April 30, 2018, to identify patients with a clinically indicated TTE performed during or within 1 day of hospitalization.[25,26] We excluded patients who did not have available data to calculate the TASV/RVSP ratio.

Data Sources

We recorded demographic, vital sign, laboratory, clinical, and outcome data, as well as procedures and therapies performed during the CICU and hospital stay; invasive hemodynamic data, physical examination, symptoms, imaging, and ECG data were not available.[27–31] All relevant data were extracted electronically from the medical record using the Multidisciplinary Epidemiology and Translational Research in Intensive Care Data Mart, a repository storing clinical data from all intensive care unit admissions at the Mayo Clinic Rochester.[32] The admission value of all vital signs, clinical measurements, and laboratory values was defined as either the first value recorded after CICU admission or the value recorded closest to CICU admission.[30] Admission diagnoses were defined as all *International Classification of Diseases, Ninth Revision* (*ICD-9*), diagnostic codes

on the day of CICU admission and 1 day before or after.[25]

Severity of Illness Scores

The Acute Physiology and Chronic Health Evaluation III score, Acute Physiology and Chronic Health Evaluation IV, which predicted hospital mortality, and Sequential Organ Failure Assessment score were automatically calculated for all patients using data from the first 24 hours of CICU admission using previously validated electronic algorithms, with missing variables imputed as normal as the default.[27–31] The Charlson Comorbidity Index and individual comorbidities were extracted from the medical record using a previously validated electronic algorithm.[33]

Echocardiographic Data

The Mayo Clinic Echocardiography Database was queried, and the TTE performed closest to the date of CICU admission (either before or after) was identified. Vital signs at the time of the TTE were recorded. Numeric variables were extracted from the database, as listed in Table S1. One left ventricular ejection fraction (LVEF) value for each patient was determined using a hierarchical approach: volumetric LVEF, calculated using the Simpson biplane method, was preferred, followed by 2-dimensional and linear calculated LVEF, followed by visual estimation if these other methods were unavailable. The right atrial pressure (RAP) was estimated on the basis of the size and collapsibility of the inferior vena cava; if an invasive measurement of RAP was available at the time of TTE, this was substituted. The RVSP was estimated as follows: RAP+[4×(peak TR velocity)^2], based on spectral Doppler (Table S2). The TASV/RVSP ratio was calculated as the ratio of TASV by tissue Doppler imaging (in cm/s)/the RVSP (in mm Hg). As a simplified version of the TASV/RVSP ratio, the ratio of TASV/TR velocity was also calculated. If TAPSE was available, the TAPSE/RVSP ratio was calculated.

Statistical Analysis

CICU, hospital, and 1-year mortality were determined using electronic review of health records. Because there is no commonly accepted normal range or established cutoff for the TASV/RVSP ratio, patients were grouped by TASV/RVSP quintiles. Categorical variables are reported as number (percentage), and the Pearson χ^2 test was used to compare groups; trends across TASV/RVSP quintiles were analyzed using the Cochran-Armitage trend test. Continuous variables are reported as mean±SD, and the Wilcoxon rank-sum test was used to compare groups. Trends across TASV/RVSP quintiles were analyzed using linear regression. Pearson *r* correlation coefficients were calculated between TASV/RVSP and other TTE variables. Logistic regression was used to determine the association between the TASV/RVSP ratio and hospital mortality, and receiver-operator characteristic curves were constructed to determine area under the receiver-operator characteristic curve (AUC) values, with 95% CIs generated using 1000-sample bootstrapping; the optimal cutoff for predicting hospital mortality was defined as the highest value of the Youden J index (sensitivity+specificity–1). AUC values were compared using the De Long test. Multivariable analysis was performed using logistic regression, with 24 clinically relevant covariates selected a priori, including demographics, comorbidities, illness severity, admission diagnoses, and the use of critical care therapies and procedures. Separate multivariable logistic regression models were generated, using either the TASV/RVSP ratio itself (per 0.1 unit) or the TASV/RVSP quintile as a continuous variable. Interaction terms between the TASV/RVSP ratio and admission diagnoses of interest were added to the multivariable logistic regression model. Survival up to 1 year was evaluated using Kaplan-Meier survival analysis, with TASV/RVSP quintiles compared using the log-rank test. Cox proportional-hazards analysis was used to determine predictors of postdischarge mortality up to 1 year in hospital survivors, adjusting for the same variables as the multivariable logistic regression model. The proportional-hazards assumption was confirmed on the basis of the final multivariable Cox model. Two-tailed $P<0.05$ was considered statistically significant. Statistical analyses were performed using JMP Pro version 14.1.0 (SAS Institute, Cary, NC).

RESULTS

Study Population

Of 12 428 potentially eligible unique CICU patient admissions, 8169 were excluded (2138 without a TTE during or within 1 day before or after hospitalization and 6031 patients whose TTE did not have available data for TASV/RVSP ratio), leaving 4259 patients in the final study population (Figure 1). Patients who were included in the final study population differed significantly from patients who were excluded from the study (Table 1); in particular, included patients were older, had a higher prevalence of acute coronary syndrome (ACS) and heart failure (HF), and had greater use of coronary angiography and percutaneous coronary intervention. The mean age of the final study population was 69.3±14.6 years, and 40.1% were women. Admission diagnoses (not mutually exclusive) in the final study population included ACS in 55.5%, HF in 51.5%, respiratory failure in 24.4%,

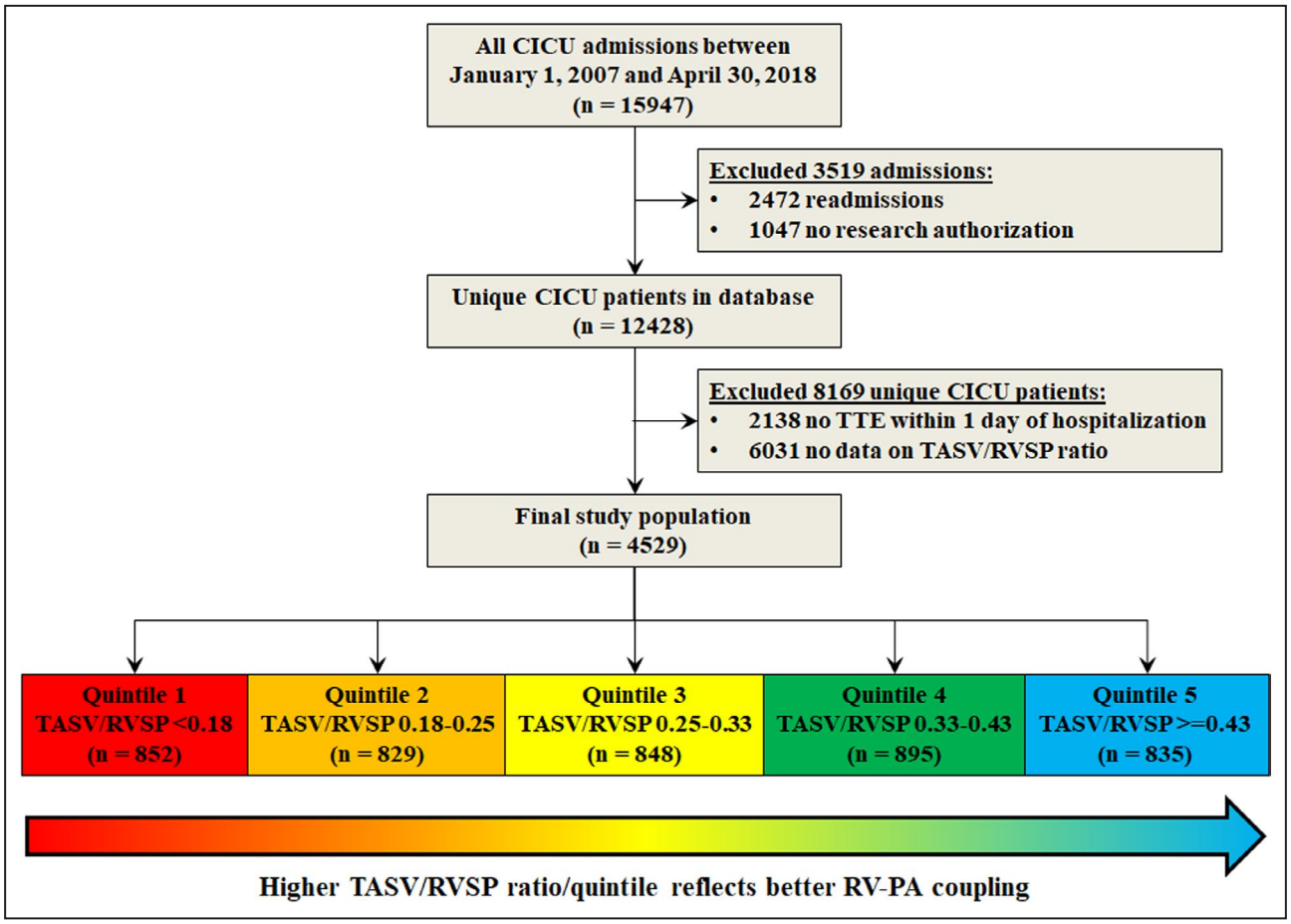

Figure 1. Flow diagram demonstrating inclusion and exclusion criteria for the final study population, and composition of tricuspid annular peak systolic tissue Doppler velocity (TASV)/right ventricular systolic pressure (RVSP) quintiles.
CICU indicates cardiac intensive care unit; PA, pulmonary artery; RV, right ventricular; and TTE, transthoracic echocardiography.

cardiogenic shock in 12.4%, cardiac arrest in 11.0%, and sepsis in 6.3% (Table 1).

Definition of TASV/RVSP Quintiles

The TASV/RVSP ratio quintiles were defined as follows: quintile 1, <0.18; quintile 2, 0.18 to 0.25; quintile 3, 0.25 to 0.33; quintile 4, 0.33 to 0.43; and quintile 5, ≥0.43 (with higher TASV/RVSP reflecting better RV-PA coupling); the mean TASV/RVSP ratio was 0.31±0.14, with a median of 0.29 (interquartile range, 0.19–0.4). Patient characteristics differed significantly across quintiles of TASV/RVSP ratio (Table 2). Patients with better RV-PA coupling (ie, higher TASV/RVSP quintiles) were younger and less likely to be women, had lower severity of illness and less use of critical care therapies, and had fewer comorbidities and critical care admission diagnoses (Table 2).

Cardiac Structure and Function by TTE

TTE was performed within 1 day of CICU admission in 3498 (82.1%) patients, including 1492 (35.0%) with TTE performed on the day of CICU admission. Measured TTE variables differed substantially across TASV/RVSP ratio quintiles (Table 3), with trends reflecting better biventricular function and lower biventricular filling pressures at higher TASV/RVSP ratio quintiles (Figure S1A and S1B). TASV/RVSP ratio varied as a function of admission diagnosis, being highest in patients with ACS and lower in patients with HF, cardiogenic shock, sepsis, or respiratory failure. TAPSE was available in 1231 (28.9%) patients, and TAPSE correlated with TASV (Pearson r=0.70; P<0.001). As expected, the TAPSE/RVSP ratio correlated strongly with TASV/RVSP ratio (Pearson r=0.88; P<0.001; Figure S2). Qualitative RV function was reported for 2787 (65.4%) patients (Table 3), including 855 (30.7%) with moderate or greater RV dysfunction. As expected, the prevalence of qualitative RV dysfunction increased with lower TASV/RVSP quintile (P<0.001).

Hospital Mortality: Univariable Analyses

Hospital mortality occurred in 306 (7.2%) patients, including 191 (4.5%) who died in the CICU. Patients who died in the hospital had a lower TASV/RVSP ratio (0.21±0.11 versus 0.31±0.15; P<0.001), resulting from

Table 1. Baseline Characteristics, Comorbidities, Admission Diagnoses, Therapies, Selected Echocardiographic Variables, and Outcomes of Patients Who Were Included and Excluded From the Final Study Population

Variable	Final Study Population (n=4529)	Excluded Patients (n=8169)	*P* Value
Demographics and outcomes			
Age, y	69.3±14.6	66.7±15.4	<0.001
Female sex	1706 (40.1)	2980 (36.5)	<0.001
White race	3941 (92.5)	7525 (92.1)	0.41
CICU length of stay, d	2.6±3.8	2.4±4.5	<0.001
Hospital length of stay, d	7.6±10.3	8.2±14.7	0.03
CICU mortality	191 (4.5)	525 (6.4)	<0.001
Hospital mortality	306 (7.2)	843 (10.3)	<0.001
1-y mortality	919 (21.6)	1920 (23.2)	0.02
Comorbidities			
Charlson Comorbidity Index	2.3±2.6	2.4±2.7	<0.001
History of MI	746 (17.6)	1554 (19.1)	0.04
History of HF	755 (17.8)	1766 (21.7)	<0.001
History of DM	1153 (27.1)	2391 (29.3)	0.01
History of lung disease	795 (18.7)	1615 (19.8)	0.14
History of CKD	812 (19.1)	1749 (21.4)	0.002
Prior dialysis	167 (3.9)	453 (5.6)	<0.001
Admission diagnoses*			
ACS	2342 (55.5)	2896 (35.8)	<0.001
HF	2173 (51.5)	3835 (47.4)	<0.001
Shock	638 (15.1)	1221 (15.1)	0.96
CS	524 (12.4)	974 (12.0)	0.53
Cardiac arrest	464 (11.0)	1015 (12.5)	0.01
Respiratory failure	1031 (24.4)	1955 (24.1)	0.73
Sepsis	268 (6.3)	512 (6.3)	0.95
Procedures and therapies			
Vasopressors	808 (19.0)	1864 (22.8)	<0.001
Inotropes	330 (7.7)	820 (10.0)	<0.001
Invasive ventilator	582 (13.7)	1452 (17.8)	<0.001
Noninvasive ventilator	661 (15.5)	1262 (15.4)	0.92
Dialysis in CICU	176 (4.1)	418 (5.1)	0.01
CRRT	89 (2.1)	155 (1.9)	0.46
IABP in CICU	356 (8.4)	695 (8.5)	0.78
PAC in CICU	383 (9.0)	815 (10.0)	0.08
Coronary angiogram	2744 (64.4)	4510 (55.2)	<0.001
PCI	1777 (41.7)	2543 (31.1)	<0.001
RBC transfusion	410 (9.6)	983 (12.0)	<0.001
In-hospital CPR	95 (2.2)	222 (2.7)	0.09
Severity of illness scores			
APACHE-III score	60.2±23.7	61.0±25.8	0.54
APACHE-IV predicted mortality, %	16.4±18.6	17.1±20.3	0.09
Day 1 SOFA score	3.3±3.1	3.6±3.2	<0.001
Braden skin score	17.9±3.2	17.6±3.4	<0.001
Vital signs at TTE			
TTE within 1 d of hospitalization	4259 (100)	1786 (22.8)	<0.001
TTE within 1 d of CICU admission	3498 (82.1)	3946 (48.3)	<0.001
Systolic BP, mm Hg	117.5±21.1	118.7±24.0	0.05
Diastolic BP, mm Hg	65.1±13.9	65.6±14.7	0.16
Heart rate, BPM	74.6±17.7	79.6±21.5	<0.001
Atrial fibrillation	579 (14.5)	1029 (18.6)	<0.001
Left ventricular systolic function			
LVEF, %	47.7±16.3	47.8±17.0	0.15
Lateral mitral s', cm/s	7.2±2.4	7.3±2.4	0.04
SV, mL	78.0±23.4	78.8±24.5	0.43
SVI, mL/m^2	40.2±11.3	39.9±12.0	0.02
LVSWI, g×min/m^2	37.7±13.9	38.8±13.9	0.002
Systemic hemodynamics			
CO, L/min	5.6±1.6	5.7±1.7	0.003
CI, L/min per m^2	2.9±0.8	2.9±0.8	0.85
CPO, W	1.03±0.35	1.07±0.38	<0.001
Pressure-adjusted heart rate, bpm	9.4±6.6	9.7±7.1	0.25
Left ventricular diastolic function			
Mitral E velocity, m/s	0.84±0.29	0.82±0.30	<0.001
Mitral E/A ratio	1.23±0.72	1.17±0.68	<0.001
Mitral e' velocity, cm/s	5.9±2.3	6.1±2.4	0.03
Mitral E/e' ratio	16.4±9.2	15.6±8.8	<0.001
RV function			
RV function (qualitative)			<0.001
Normal or borderline	1097 (39.4)	1685 (46.0)	
Mild dysfunction	964 (34.6)	1134 (30.9)	
Moderate or greater	726 (26.0)	847 (23.1)	
Estimated RAP, mm Hg	9.7±5.2	9.8±5.3	0.97
TR velocity, m/s	2.78±0.53	2.84±0.58	<0.001
Estimated RVSP, mm Hg	41.9±15.4	44.2±16.6	<0.001
Tricuspid s' velocity, cm/s	11.3±3.5	11.7±3.5	<0.001
TASV/RVSP ratio	0.31±0.14	0.29±0.15	<0.001
TAPSE	17.3±5.3	18.0±5.5	0.002
TAPSE/RVSP ratio	0.19±0.27	0.17±0.23	<0.001
TASV/TR velocity ratio	4.2±1.5	3.9±1.6	<0.001

Data displayed as number (percentage) for categorical variables or mean±SD for continuous variables. *P* value is for the Pearson χ^2 test (categorical variables) or Wilcoxon rank-sum test (continuous variables) comparing included and excluded patients. ACS indicates acute coronary syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; BP, blood pressure; BPM, beats per minute; CI, cardiac index; CICU, cardiac intensive care unit; CKD, chronic kidney disease; CO, cardiac output; CPO, cardiac power output; CPR, cardiopulmonary resuscitation; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; DM, diabetes mellitus; e', peak early diastolic tissue Doppler velocity; E/e', ratio of peak early transmitral spectral Doppler velocity to peak early diastolic tissue Doppler velocity; E, peak early transmitral spectral Doppler velocity; E/A, ratio of early to atrial peak transmitral spectral Doppler velocity; HF, heart failure; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; LVSWI, left ventricular stroke work index; MI, myocardial infarction; PAC, pulmonary artery catheter; PCI, percutaneous coronary intervention; RAP, right atrial pressure; RBC, red blood cell; RV, right ventricular; RVSP, RV systolic pressure; s', peak systolic tissue Doppler velocity; SOFA, Sequential Organ Failure Assessment; SV, stroke volume; SVI, SV index; TAPSE, tricuspid annular plane systolic excursion; TASV, tricuspid annular peak systolic tissue Doppler velocity; TR, tricuspid regurgitation; and TTE, transthoracic echocardiography.

*Admission diagnoses are not mutually exclusive and sum to >100%.

Table 2. Baseline Characteristics, Comorbidities, Admission Diagnoses, and Therapies of Patients, According to TASV/RVSP Quintiles, Where Higher Quintiles Reflect Better RV-PA Coupling

Variable	Quintile 1 (n=852)	Quintile 2 (n=829)	Quintile 3 (n=848)	Quintile 4 (n=895)	Quintile 5 (n=835)	*P* Value
Demographics						
Age, y	71.3±14.5	72.5±14.4	71.2±14.0	68.1±13.7	63.5±14.8	<0.001
Female sex	367 (43.1)	359 (43.3)	354 (41.8)	339 (37.9)	287 (34.4)	<0.001
White race	762 (89.4)	765 (92.3)	800 (94.3)	835 (93.3)	779 (93.3)	0.002
Comorbidities						
Charlson Comorbidity Index	3.3±2.9	2.7±2.6	2.3±2.4	1.7±2.1	1.4±2.1	<0.001
History of MI	186 (21.9)	172 (20.8)	150 (17.7)	139 (15.6)	99 (11.9)	<0.001
History of HF	329 (38.7)	195 (23.6)	113 (13.4)	79 (8.8)	39 (4.7)	<0.001
History of DM	331 (38.9)	255 (30.8)	222 (26.2)	205 (23.0)	140 (16.8)	<0.001
History of lung disease	214 (25.2)	198 (23.9)	156 (18.4)	132 (14.8)	95 (11.4)	<0.001
History of CKD	284 (33.4)	207 (25.0)	155 (18.3)	104 (11.6)	62 (7.4)	<0.001
Prior dialysis	63 (7.4)	51 (6.2)	19 (2.2)	19 (2.1)	15 (1.8)	<0.001
Admission diagnoses*						
ACS	305 (35.8)	391 (47.5)	493 (58.7)	580 (65.5)	573 (69.7)	<0.001
HF	714 (83.9)	562 (68.3)	419 (49.9)	301 (34.0)	177 (21.5)	<0.001
Shock	180 (21.2)	182 (22.1)	125 (14.9)	88 (9.9)	63 (7.7)	<0.001
CS	153 (18.0)	152 (18.5)	104 (12.4)	65 (7.3)	50 (6.1)	<0.001
Cardiac arrest	93 (10.9)	109 (13.2)	101 (12.0)	96 (10.8)	65 (7.9)	0.015
Respiratory failure	320 (37.6)	283 (34.4)	209 (24.9)	149 (16.8)	70 (8.5)	<0.001
Sepsis	74 (8.7)	77 (9.4)	57 (6.8)	41 (4.6)	19 (2.3)	<0.001
Procedures and therapies						
Vasopressors	249 (29.2)	214 (25.8)	152 (17.9)	125 (14.0)	68 (8.1)	<0.001
Inotropes	144 (16.9)	107 (12.9)	45 (5.3)	23 (2.6)	11 (1.3)	<0.001
Invasive ventilator	166 (19.5)	159 (19.2)	123 (14.5)	90 (10.1)	44 (5.3)	<0.001
Noninvasive ventilator	209 (24.5)	171 (20.6)	135 (15.9)	95 (10.6)	51 (6.1)	<0.001
Dialysis in CICU	81 (9.5)	51 (6.2)	22 (2.6)	11 (1.2)	11 (1.3)	<0.001
CRRT	42 (4.9)	27 (3.3)	14 (1.6)	2 (0.2)	4 (0.5)	<0.001
IABP in CICU	77 (9.0)	87 (10.5)	73 (8.6)	61 (6.8)	58 (7.0)	0.009
PAC in CICU	142 (16.7)	115 (13.9)	59 (7.0)	45 (5.0)	22 (2.6)	<0.001
Coronary angiogram	455 (53.4)	492 (59.4)	544 (64.2)	635 (71.0)	618 (74.0)	<0.001
PCI	203 (23.8)	262 (31.6)	369 (43.5)	475 (53.1)	468 (56.0)	<0.001
RBC transfusion	114 (13.4)	103 (12.4)	81 (9.6)	71 (7.9)	41 (4.9)	<0.001
In-hospital CPR	30 (3.5)	22 (2.7)	14 (1.6)	15 (1.7)	14 (1.7)	0.004
Severity of illness scores						
APACHE-III score	70.3±23.9	67.4±24.1	60.8±22.5	54.2±21.3	48.7±19.5	<0.001
APACHE-IV predicted hospital mortality, %	23.7±21.0	21.3±20.8	16.4±17.8	11.9±15.0	8.8±12.5	<0.001
Day 1 SOFA score	4.8±3.3	4.1±3.3	3.2±2.9	2.5±2.5	1.9±2.2	<0.001
Braden skin score	16.9±3.2	17.3±3.3	17.8±3.2	18.5±3.0	19.1±2.8	<0.001
Outcomes						
CICU length of stay, d	3.5±6.3	3.0±4.4	2.4±2.1	2.1±1.9	1.8±1.7	<0.001
Hospital length of stay, d	11.0±14.0	9.5±11.7	7.0±9.3	5.7±7.1	4.7±6.1	<0.001
CICU mortality	93 (10.9)	40 (4.8)	34 (4.0)	17 (1.9)	7 (0.8)	<0.001
Hospital mortality	131 (15.4)	84 (10.1)	47 (5.5)	33 (3.7)	11 (1.3)	<0.001
1-y Mortality	359 (42.1)	234 (28.2)	162 (19.1)	103 (11.5)	61 (7.3)	<0.001

Data displayed as number (percentage) for categorical variables or mean±SD for continuous variables. *P* value is for the Cochran-Armitage trend test (categorical variables) or linear regression (continuous variables) across TASV/RVSP ratio quintiles. ACS indicates acute coronary syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; CICU, cardiac intensive care unit; CKD, chronic kidney disease; CPR, cardiopulmonary resuscitation; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; DM, diabetes mellitus; HF, heart failure; IABP, intra-aortic balloon pump; MI, myocardial infarction; PA, pulmonary artery; PAC, PA catheter; PCI, percutaneous coronary intervention; RBC, red blood cell; RV, right ventricular; RVSP, RV systolic pressure; SOFA, Sequential Organ Failure Assessment; and TASV, tricuspid annular peak systolic tissue Doppler velocity.

*Admission diagnoses are not mutually exclusive and sum to >100%.

Table 3. Echocardiographic Characteristics of Patients, According to TASV/RVSP Quintiles, Where Higher Quintiles Reflect Better RV-PA Coupling

Variable	No. With Data	Quintile 1 (n=852)	Quintile 2 (n=829)	Quintile 3 (n=848)	Quintile 4 (n=895)	Quintile 5 (n=835)	*P* Value
Vital signs at TTE							
Systolic BP, mm Hg	4227	114.0±21.8	116.2±22.0	118.7±21.4	119.0±20.3	119.7±19.7	<0.001
Diastolic BP, mm Hg	4223	63.9±14.4	63.9±14.5	64.3±14.1	66.0±13.4	67.3±12.6	<0.001
Heart rate, BPM	4093	78.7±18.9	77.4±18.5	74.0±18.0	72.3±16.5	70.5±15.2	<0.001
Atrial fibrillation	4002	239 (30.7)	163 (21.3)	100 (12.6)	58 (6.8)	19 (2.4)	<0.001
Left ventricular systolic function							
LVEF, %	4229	40.8±18.5	43.3±17.2	48.2±15.1	51.5±13.7	54.3±12.3	<0.001
Lateral mitral s', cm/s	3140	5.8±2.2	6.4±2.1	7.2±2.3	7.6±2.2	8.3±2.5	<0.001
SV, mL	4089	67.6±23.7	71.9±23.1	80.1±22.8	84.1±22.0	86.0±19.6	<0.001
SVI, mL/m^2	4065	35.2±11.8	37.6±11.6	41.3±11.1	43.0±10.2	43.6±9.0	<0.001
LVSWI, g×min/m^2	3512	29.5±12.3	33.7±14.1	38.1±13.2	41.5±13.2	43.4±12.1	<0.001
Systemic hemodynamics							
CO, L/min	4061	5.1±1.6	5.3±1.6	5.7±1.6	5.9±1.5	5.9±1.4	<0.001
CI, L/min per m^2	4043	2.6±0.8	2.8±0.8	2.9±0.8	3.0±0.7	3.0±0.7	<0.001
CPO, W	4028	0.91±0.33	0.96±0.35	1.04±0.35	1.09±0.35	1.11±0.33	<0.001
Pressure-adjusted heart rate	4068	15.0±6.9	12.0±6.8	8.8±5.7	6.3±4.1	5.0±2.9	<0.001
Left ventricular diastolic function							
Mitral E velocity, m/s	3764	1.0±0.3	0.9±0.3	0.9±0.3	0.8±0.2	0.7±0.2	<0.001
Mitral E/A ratio	3089	1.7±1.0	1.4±0.9	1.2±0.6	1.1±0.5	1.1±0.5	<0.001
Mitral e' velocity, cm/s	3831	4.8±2.0	5.4±2.1	6.0±2.2	6.2±2.1	7.0±2.4	<0.001
Mitral E/e' ratio	3664	23.6±12.1	19.0±9.1	16.0±7.9	13.6±6.1	11.4±4.8	<0.001
RV function							
RV function (qualitative)	2787						<0.001
Normal or borderline		82 (10.6)	187 (29.2)	240 (45.7)	309 (62.9)	279 (77.7)	
Mild dysfunction		277 (35.9)	266 (41.6)	204 (38.9)	151 (30.8)	66 (18.4)	
Moderate or greater		465 (60.2)	281 (34.1)	110 (21.0)	42 (8.6)	20 (5.6)	
Estimated RAP, mm Hg	4259	14.7±4.6	12.0±4.9	9.4±4.7	7.0±3.4	5.7±2.1	<0.001
TR velocity, m/s	4259	3.3±0.6	3.0±0.5	2.8±0.4	2.6±0.3	2.4±0.3	<0.001
Estimated RVSP, mm Hg	4259	59.7±16.9	47.9±11.3	40.6±9.0	33.7±7.0	28.1±5.8	<0.001
Tricuspid s' velocity, cm/s	4259	7.6±2.3	10.0±2.4	11.6±2.5	12.7±2.5	14.7±3.0	<0.001
TASV/RVSP ratio	4259	0.13±0.03	0.21±0.02	0.29±0.02	0.38±0.03	0.53±0.09	<0.001
TAPSE	1231	13.7±3.8	16.5±4.7	18.7±4.7	19.9±4.3	22.9±4.6	<0.001
TAPSE/RVSP ratio	1231	0.24±0.08	0.35±0.08	0.48±0.11	0.64±0.13	0.85±0.19	<0.001
TASV/TR velocity ratio	4259	2.3±0.5	3.4±0.5	4.2±0.6	4.9±0.6	6.2±1.0	<0.001

Data displayed as number (percentage) for categorical variables or mean±SD for continuous variables. *P* value is for the Cochran-Armitage trend test (categorical variables) or linear regression (continuous variables) across TASV/RVSP ratio quintiles. BP indicates blood pressure; BPM, beats per minute; CI, cardiac index; CO, cardiac output; CPO, cardiac power output; E, peak early transmitral spectral Doppler velocity; E/A, ratio of early to atrial peak transmitral spectral Doppler velocity; e', peak early diastolic tissue Doppler velocity; E/e', ratio of peak early transmitral spectral Doppler velocity to peak early diastolic tissue Doppler velocity; LVEF, left ventricular ejection fraction; LVSWI, left ventricular stroke work index; PA, pulmonary artery; RAP, right atrial pressure; RV, right ventricular; RVSP, RV systolic pressure; s', peak systolic tissue Doppler velocity; SV, stroke volume; SVI, SV index; TAPSE, tricuspid annular plane systolic excursion; TASV, tricuspid annular peak systolic tissue Doppler velocity; TR, tricuspid regurgitation; and TTE, transthoracic echocardiography.

both lower TASV (10.1±3.9 versus 11.6±3.4 cm/s; *P*<0.001) and higher RVSP (50.9±18.1 versus 42.1±15.5 mm Hg; *P*<0.001). Patients in the lowest 2 quintiles of TASV/RVSP ratio accounted for most inpatient deaths (quintile 1, 42.8%; and quintile 2, 27.4%), whereas only 3.6% of inpatient deaths were in TASV/RVSP ratio quintile 5. A clear stepwise decrease in CICU and hospital mortality was observed with increasing TASV/RVSP ratio quintile (unadjusted odds ratio [OR], 0.560 per each higher TASV/RVSP quintile; 95% CI, 0.507–0.617; *P*<0.001; Figure S3).

TASV/RVSP ratio was inversely associated with hospital mortality (unadjusted unit OR, 0.516 per each 0.1 higher TASV/RVSP ratio; 95% CI, 0.461–0.578; *P*<0.001; AUC, 0.719; 95% CI, 0.690–0.744), with an optimal cutoff value of 0.25 for prediction of hospital mortality corresponding

to the 40th percentile. Inverse relationships between TASV/RVSP ratio and mortality were observed in patients with each admission diagnosis (Figure 2). The association between TASV/RVSP ratio and mortality differed as a function of admission diagnosis (Table 4), being strongest (AUC, 0.73) for patients with ACS and weakest (AUC, 0.58; *P*=0.08) for patients with sepsis.

Hospital Mortality Discrimination by TTE

The AUC value for hospital mortality for the TASV/RVSP ratio was higher than that for TASV (AUC, 0.64; 95% CI, 0.61–0.68; *P*<0.001 by De Long test), RVSP (AUC, 0.68; 95% CI, 0.65–0.71; *P*=0.004 by De Long test), or TASV/TR velocity ratio (AUC, 0.69; 95% CI, 0.65–0.72; *P*<0.001 by De Long test). Among the 1231 (28.9%) with available data for the TAPSE/RVSP ratio, the AUC value for hospital mortality (0.68; 95% CI, 0.63–0.73) was similar to that observed for the TASV/RVSP ratio in this group (*P*=0.47 by De Long test). Addition of the TASV/RVSP ratio to the Acute Physiology and Chronic Health Evaluation III score alone resulted in an improvement in discrimination for hospital mortality (AUC, 0.822 versus 0.764; *P*<0.001 by De Long test).

Hospital Mortality: Multivariable Analyses

After multivariable adjustment (Table 5), TASV/RVSP ratio remained inversely associated with hospital mortality (adjusted unit OR, 0.676 per each 0.1 higher; 95% CI, 0.582–0.786; *P*<0.001). Discrimination for hospital mortality by the multivariable model was excellent with or without inclusion of the TASV/RVSP ratio in the model (AUC, 0.914 versus 0.909, respectively; *P*=0.11 by De Long test). Each higher TASV/RVSP ratio quintile was associated with lower adjusted hospital mortality (adjusted OR, 0.714 per each higher TASV/RVSP ratio quintile; 95% CI, 0.627–0.814; *P*<0.001); each other TASV/RVSP quintile had lower hospital-adjusted mortality than quintile 1 (all *P*<0.001; Figure 3A).

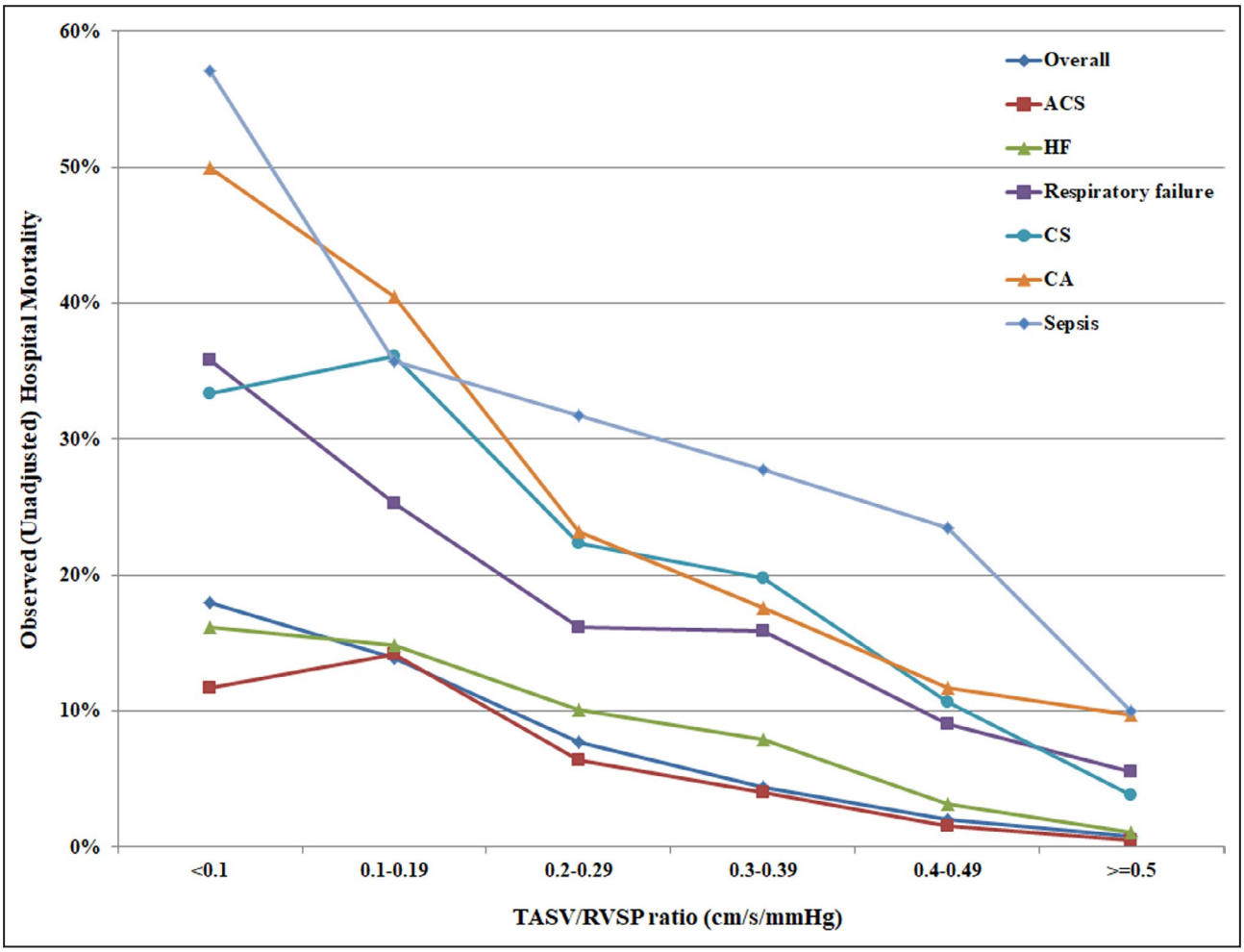

Figure 2. Hospital mortality as a function of tricuspid annular peak systolic tissue Doppler velocity (TASV)/right ventricular systolic pressure (RVSP) ratio among patients, according to admission diagnosis.
A higher TASV/RVSP ratio reflects better RV-PA coupling. All *P*<0.001 for trends. ACS indicates acute coronary syndrome; CA, cardiac arrest; CS, cardiogenic shock; and HF, heart failure.

Table 4. Discrimination for Hospital Mortality by the TASV/RVSP Ratio (per Each 0.1 Higher TASV/RVSP Ratio) Among Patients, According to Admission Diagnosis (Admission Diagnoses Were Not Mutually Exclusive)

Admission Diagnosis	Unadjusted OR per 0.1	95% CI	AUC	*P* Value
Acute coronary syndrome	0.489	0.412–0.580	0.734	<0.0001
Cardiac arrest	0.604	0.497–0.733	0.686	<0.0001
Cardiogenic shock	0.636	0.518–0.781	0.648	<0.0001
Heart failure	0.650	0.564–0.748	0.626	<0.0001
Respiratory failure	0.654	0.556–0.770	0.621	<0.0001
Sepsis	0.806	0.633–1.027	0.583	0.08
Shock (any type)	0.666	0.560–0.792	0.634	<0.0001

Data displayed as unadjusted OR and 95% CI values, with the AUC and *P* value for patients with each admission diagnosis. AUC indicates area under the receiver-operator characteristic curve; OR, odds ratio; RVSP, right ventricular systolic pressure; and TASV, tricuspid annular peak systolic tissue Doppler velocity.

A higher TASV/RVSP ratio remained associated with lower hospital mortality in patients with (adjusted OR, 0.741; 95% CI, 0.617–0.890; *P*=0.001) and without (adjusted OR, 0.563; 95% CI, 0.423–0.749; *P*<0.001) left ventricular (LV) systolic dysfunction. Likewise, the TASV/RVSP ratio remained associated with hospital mortality after adjusting for LVEF and mitral ratio of peak early transmitral spectral Doppler velocity to peak early diastolic tissue Doppler velocity (E/e') ratio (adjusted OR, 0.759; 95% CI, 0.639–0.902; *P*=0.002); neither LVEF nor mitral E/e' ratio was associated with adjusted hospital mortality (*P*>0.1). We observed a significant statistical interaction (*P*=0.01) between an admission diagnosis of sepsis and TASV/RVSP for prediction of hospital mortality on multivariable logistic regression; there were no significant interactions with other admission diagnoses.

One-Year Mortality: Univariable Analyses

A total of 919 (21.6%) patients died within 1 year after CICU admission, including 613 (15.5%) of the 3953 hospital survivors plus the 306 patients who died during hospitalization; 428 (10.0%) had <1 year of follow-up. The TASV/RVSP ratio was inversely associated with 1-year mortality in hospital survivors (unadjusted unit hazard ratio [HR], 0.604 per each 0.1 higher TASV/RVSP ratio; 95% CI, 0.562–0.647; *P*<0.001). One-year survival was progressively higher in each higher TASV/RVSP quintile by Kaplan-Meier analysis, both in the entire cohort and among hospital survivors (*P*<0.001 by log-rank; Figure 4).

One-Year Mortality: Multivariable Analyses

After multivariable adjustment (Table 6), the TASV/RVSP ratio remained inversely associated with 1-year mortality in hospital survivors (adjusted unit HR, 0.829 per each 0.1 higher; 95% CI, 0.767–0.895; *P*<0.001). Each higher TASV/RVSP quintile was associated with lower adjusted 1-year mortality among hospital survivors than quintile 1 (all *P*<0.01; Figure 3B). A higher TASV/RVSP ratio remained associated with lower 1-year mortality in hospital survivors with (adjusted HR, 0.0.793 per each 0.1 higher; 95% CI, 0.714–0.879; *P*<0.001), but not those without (adjusted HR, 0.912 per each 0.1 higher; 95% CI, 0.0.806–1.031; *P*=0.14) LV systolic dysfunction. Likewise, the TASV/RVSP ratio remained associated with 1-year mortality among hospital survivors after adjusting for LVEF and mitral E/e' ratio (adjusted HR, 0.877; 95% CI, 0.804–0.957; *P*=0.003); mitral E/e' ratio (*P*=0.049) was nominally associated with higher adjusted 1-year mortality, but LVEF was not (*P*=0.13).

DISCUSSION

This is the first study examining RV-PA coupling by TTE in a cohort of critically ill patients, and one of the first studies examining the prognostic associations of the TASV/RVSP ratio by TTE. The ratio of TASV/RVSP, reflecting RV-PA coupling, is strongly and inversely related to hospital and 1-year postdischarge mortality across a broad range of patients receiving care in the CICU. Our results emphasize the importance of both PH and RV function, as reflected by impaired RV-PA coupling measured using Doppler TTE, as determinants of in-hospital and postdischarge outcomes in hospitalized patients with cardiovascular disease. Patients with higher TASV/RVSP ratio, reflecting better load-adjusted RV function, were less likely to die, even after adjusting for severity of illness and other factors known to predict outcomes. The TASV/RVSP ratio remained associated with mortality after adjustment for LV function, although the association between TASV/RVSP ratio and mortality was stronger in patients without LV systolic dysfunction. The association between TASV/RVSP ratio and mortality varied as a function of admission diagnosis, being strongest among patients with ACS and not significantly associated among patients with sepsis. This study validates the TASV/RVSP ratio as a much-needed imaging biomarker of RV-PA coupling that can be used for risk stratification in this critically ill population. Further study is required to determine whether therapeutic interventions to optimize impaired RV-PA coupling may improve outcomes in this population.

This analysis adds to a growing literature on both the importance of 2-dimensional and Doppler echocardiography and noninvasive hemodynamics for risk stratification and the adverse prognosis associated with RV dysfunction and PH in critically ill patients.[4–8,10,11,34] Prior studies have shown PH and/or RV

Table 5. Predictors of Hospital Mortality Using Unadjusted and Multivariable-Adjusted Logistic Regression

Variable	Unadjusted Logistic Regression			Multivariable-Adjusted Regression		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Demographics and comorbidities						
Age (per y)	1.016	1.007–1.025	<0.001	1.019	1.006–1.031	0.004*
Female sex	0.948	0.747–1.204	0.67	0.860	0.640–1.154	0.31
White race	0.668	0.454–0.982	0.04	0.720	0.431–1.204	0.21
Charlson Comorbidity Index	1.142	1.100–1.186	<0.001	1.041	0.988–1.098	0.13
Prior dialysis	2.388	1.535–3.715	<0.001	0.951	0.519–1.742	0.87
Admission diagnoses						
ACS	0.561	0.433–0.710	<0.001	1.021	0.724–1.440	0.91
HF	3.656	2.768–4.828	<0.001	1.009	0.693–1.467	0.96
CA	6.260	4.847–8.085	<0.001	3.039	2.074–4.455	<0.001*
Shock	9.807	7.667–12.543	<0.001	2.662	1.853–3.825	<0.001*
Respiratory failure	7.233	5.640–9.275	<0.001	1.682	1.166–2.427	0.005*
Sepsis	7.846	5.866–10.494	<0.001	1.982	1.349–2.910	<0.001*
Severity of illness						
APACHE-III score	1.043	1.039–1.048	<0.001	1.012	1.005–1.019	<0.001*
Braden skin score	0.750	0.723–0.777	<0.001	0.915	0.868–0.964	<0.001*
Procedures and therapies						
Coronary angiogram	0.437	0.346–0.552	<0.001	0.516	0.366–0.727	<0.001*
PCI	0.383	0.291–0.504	<0.001	0.860	0.584–1.269	0.45
IABP	2.940	2.162–4.000	<0.001	1.124	0.705–1.792	0.62
PAC	3.154	2.347–4.239	<0.001	0.907	0.592–1.388	0.65
Invasive ventilator	8.344	6.528–10.667	<0.001	0.712	0.458–1.106	0.13
Noninvasive ventilator	2.648	2.044–3.429	<0.001	1.111	0.788–1.567	0.55
No. of vasoactive drugs	2.789	2.495–3.117	<0.001	1.282	1.107–1.486	<0.001*
RBC transfusion	3.362	2.527–4.473	<0.001	0.776	0.519–1.161	0.22
Dialysis	8.309	5.937–11.631	<0.001	1.931	0.959–3.890	0.07
CRRT	15.317	9.924–23.642	<0.001	3.111	1.342–7.212	0.008*
IHCA	10.141	6.616–15.546	<0.001	4.138	2.348–7.292	<0.001*
TASV/RVSP ratio (per 0.1)	0.516	0.461–0.578	<0.001	0.676	0.582–0.786	<0.001*

Data are displayed as unit OR and 95% CI values. The final multivariable logistic regression model area under the receiver-operator characteristic curve value was 0.914 for hospital mortality. ACS indicates acute coronary syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; CA, cardiac arrest; CRRT, continuous renal replacement therapy; HF, heart failure; IABP, intra-aortic balloon pump; IHCA, in-hospital CA; OR, odds ratio; PAC, pulmonary artery catheter; PCI, percutaneous coronary intervention; RBC, red blood cell; RVSP, right ventricular systolic pressure; and TASV, tricuspid annular peak systolic tissue Doppler velocity.

*All listed variables were included in the final multivariable model, and * denotes variables that had $P<0.05$ in the final multivariable model.

dysfunction to be associated with worse outcomes in patients with sepsis or unselected medical intensive care unit patients.[6–8,10,11,34] The only recent study we identified examining RV-PA coupling in critically ill patients used invasive measurements to define this parameter in surgical intensive care unit patients.[34] To our knowledge, this is the first study examining the prognostic impact of noninvasively assessed PH or RV function in a mixed CICU population, further underscoring the importance of Doppler TTE assessment in patients with acute cardiovascular disease. Our results demonstrate that the TASV/RVSP ratio improves hospital mortality discrimination beyond established measures of illness severity, although the incremental improvement over a fully adjusted multivariable model is modest.

The concept of RV-PA coupling describes the adaptation of the RV to alterations in afterload.[3,35] With preserved RV-PA coupling during the early phase of chronic PH, the RV can compensate for the increased afterload by increasing its contractility, often with associated RV hypertrophy and dilatation but initially preserved systolic function.[3,35] With progression of chronic PH leading to RV failure, RV-PA uncoupling leads to a decrease in RV systolic function associated with a loss of RV longitudinal motion.[3,35] Therefore,

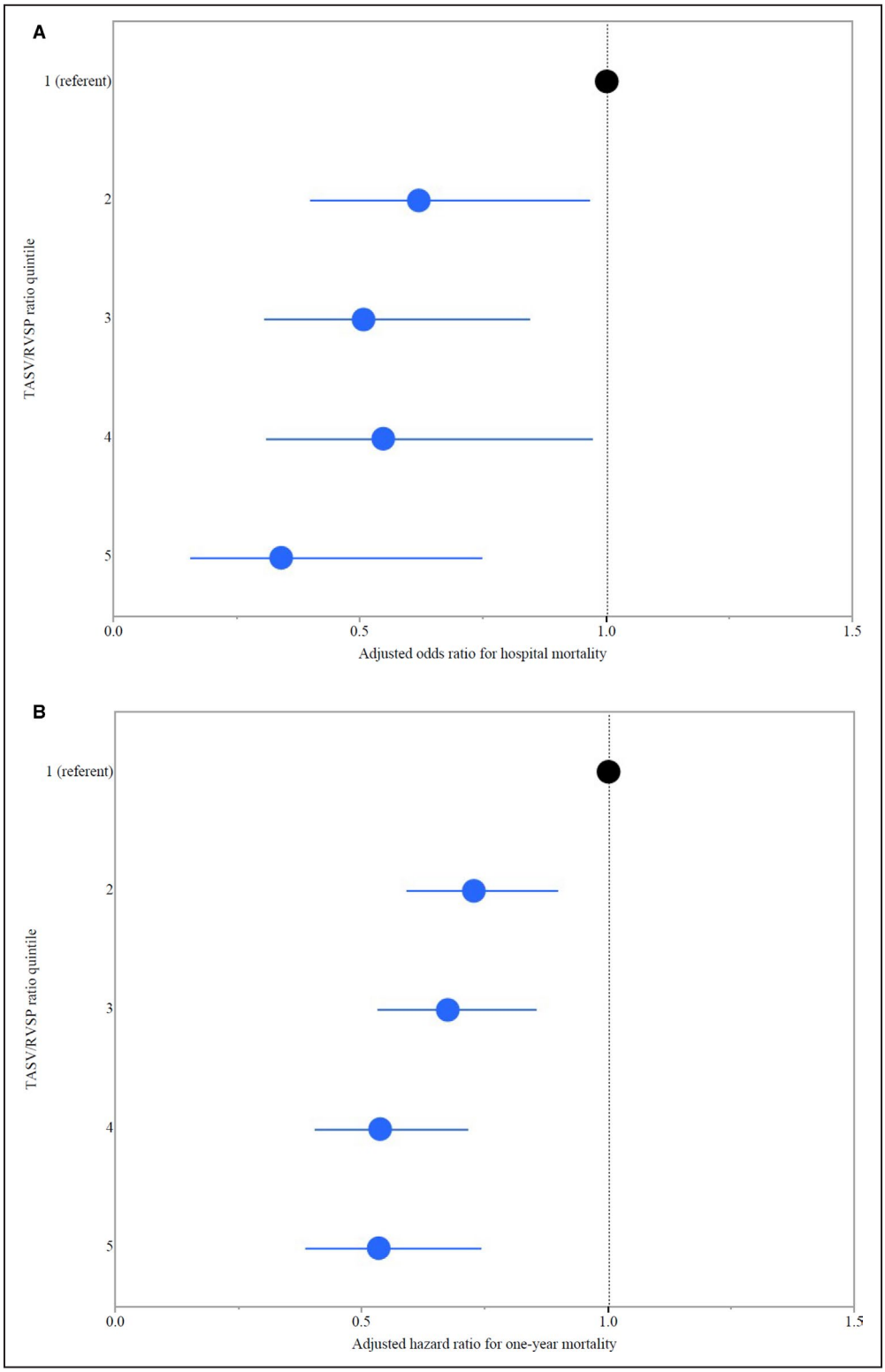

Figure 3. Forest plot demonstrating adjusted odds ratio values for hospital mortality using logistic regression (A) and adjusted hazard ratio values for 1-year mortality among hospital survivors using Cox proportional-hazards (B), according to tricuspid annular peak systolic tissue Doppler velocity (TASV)/right ventricular systolic pressure (RVSP) ratio quintile, with quintile 1 as referent.

TASV/RVSP quintiles are numbered 1 to 5, with a higher TASV/RVSP ratio quintile reflecting better right ventricular pulmonary artery coupling. All $P<0.001$.

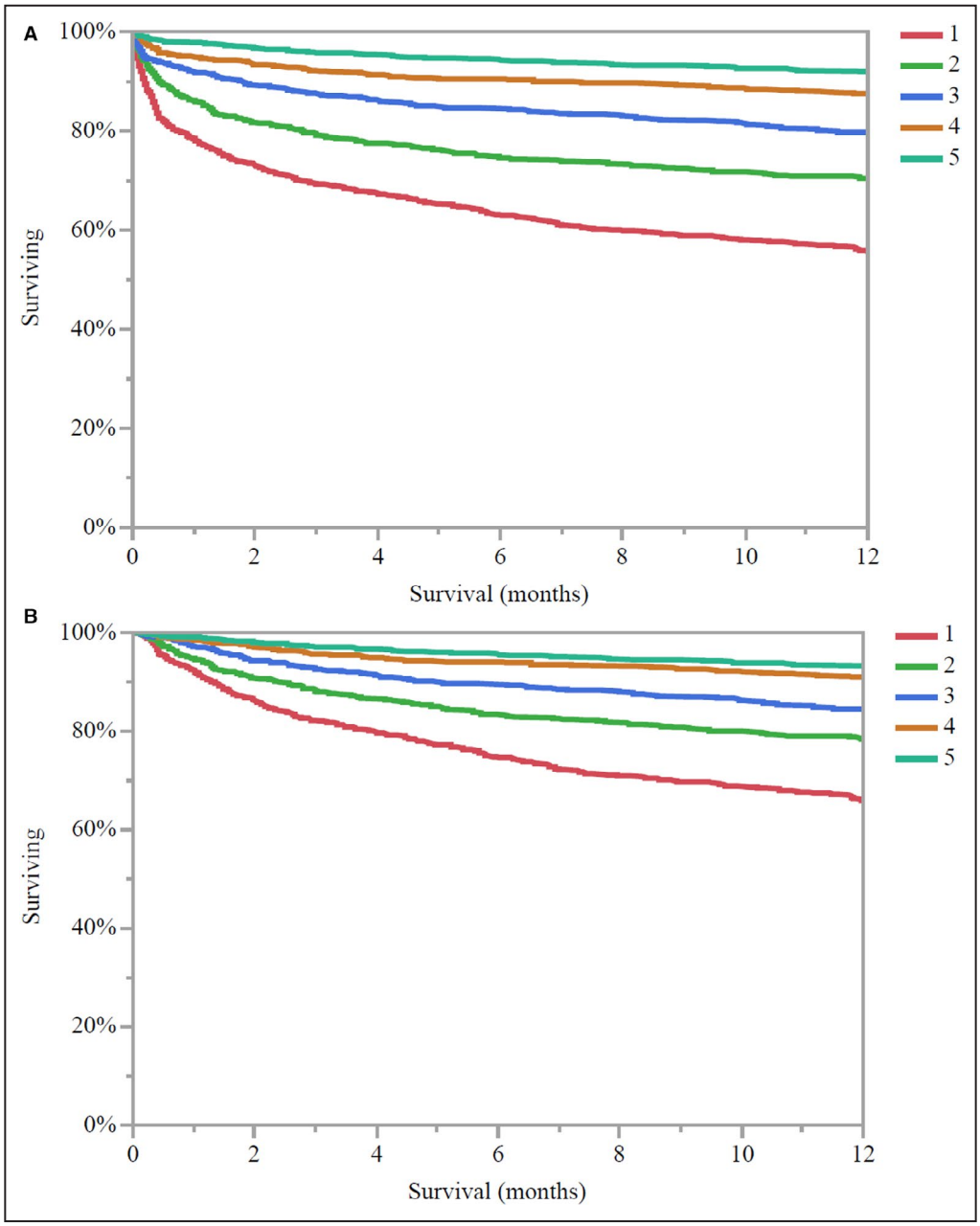

Figure 4. Kaplan-Meier curves demonstrating survival up to 1 year after cardiac intensive care unit admission as a function of tricuspid annular peak systolic tissue Doppler velocity (TASV)/right ventricular systolic pressure (RVSP) ratio quintile in the overall population (A) and among hospital survivors (B).
TASV/RVSP quintiles are numbered 1 to 5, with a higher TASV/RVSP ratio quintile reflecting better right ventricular pulmonary artery coupling. *P*<0.001 by log-rank.

the TASV/RVSP (or TAPSE/RVSP, which is strongly correlated with TASV/RVSP and performed similarly for mortality discrimination in this cohort) provides a metric reflecting RV-PA coupling by integrating both RV systolic longitudinal motion and RV afterload.[12] The TASV/RVSP ratio by Doppler TTE is easier to obtain than other proposed invasive and noninvasive measures of RV-PA coupling, including the ratio of RV end-systolic elastance/PA elastance or the ratio of RV fractional area change, end-systolic area, free wall strain, or ejection fraction using advanced imaging modalities to RVSP.[3,34,36–38] The TASV/RVSP ratio can be measured at bedside in most patients using standard equipment, permitting assessment of RV physiological features at bedside that can offer insights into prognosis even when 2-dimensional

Table 6. Predictors of 1-Year Mortality Among Hospital Survivors Using Unadjusted and Multivariable-Adjusted Cox Proportional-Hazards Analysis

	Unadjusted Cox			Multivariable-Adjusted Cox		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Demographics and comorbidities						
Age (per y)	1.042	1.035–1.048	<0.001	1.024	1.016–1.032	<0.001*
Female sex	1.028	0.876–1.208	0.73	0.845	0.716–0.996	0.05*
White race	0.977	0.712–1.342	0.89	0.835	0.600–1.161	0.28
Charlson Comorbidity Index	1.219	1.192–1.246	<0.001	1.105	1.074–1.136	<0.001*
Prior dialysis	2.914	2.198–3.862	<0.001	1.231	0.899–1.686	0.20
Admission diagnoses						
ACS	0.637	0.544–0.747	<0.001	1.263	1.043–1.528	0.02*
HF	4.164	3.434–5.049	<0.001	2.039	1.638–2.538	<0.001*
CA	0.961	0.723–1.276	0.78	0.811	0.582–1.128	0.21
Shock	1.416	1.137–1.762	0.002	0.688	0.514–0.922	0.01*
Respiratory failure	2.527	2.146–2.975	<0.001	1.290	1.041–1.599	0.02*
Sepsis	2.324	1.777–3.039	<0.001	1.029	0.765–1.384	0.85
Severity of illness						
APACHE-III score	1.026	1.023–1.029	<0.001	1.012	1.006–1.017	<0.001*
Braden skin score	0.867	0.847–0.887	<0.001	0.933	0.903–0.963	<0.001*
Procedures and therapies						
Coronary angiogram	0.432	0.369–0.506	<0.001	0.661	0.546–0.801	<0.001*
PCI	0.407	0.339–0.488	<0.001	0.722	0.582–0.895	0.003*
IABP	0.924	0.678–1.260	0.62	0.832	0.586–1.180	0.30
PAC	1.534	1.194–1.971	<0.001	1.082	0.802–1.458	0.61
Invasive ventilator	1.733	1.398–2.149	<0.001	0.672	0.495–0.911	0.01*
Noninvasive ventilator	2.207	1.840–2.647	<0.001	1.026	0.832–1.264	0.81
No. of vasoactive drugs	1.327	1.225–1.430	<0.001	1.132	1.004–1.277	0.04*
RBC transfusion	1.753	1.391–2.210	<0.001	0.959	0.744–1.235	0.74
Dialysis	3.001	2.208–4.078	<0.001	1.475	0.922–2.361	0.11
CRRT	4.459	2.913–6.828	<0.001	1.509	0.808–2.819	0.20
IHCA	1.805	1.063–3.066	0.03	1.565	0.874–2.801	0.13
TASV/RVSP ratio (per 0.1)	0.604	0.562–0.647	<0.001	0.829	0.767–0.895	<0.001*

Data are displayed as unit HR and 95% CI values. ACS indicates acute coronary syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; CA, cardiac arrest; CRRT, continuous renal replacement therapy; HF, heart failure; HR, hazard ratio; IABP, intra-aortic balloon pump; IHCA, in-hospital CA; PAC, pulmonary artery catheter; PCI, percutaneous coronary intervention; RBC, red blood cell; RVSP, right ventricular systolic pressure; and TASV, tricuspid annular peak systolic tissue Doppler velocity.

[a]All listed variables were included in the final multivariable model, and * denotes variables that had $P<0.05$ in the final multivariable model.

image quality is suboptimal and more sophisticated imaging methods are not feasible.[9]

The use of the TAPSE/RVSP ratio by echocardiography, as a proposed marker of RV-PA coupling, has been well established, and our results extend prior studies by demonstrating that the TASV/RVSP ratio by Doppler TTE is clinically feasible and useful for outcome prediction.[12] Studies have consistently associated a low TAPSE/RVSP ratio with worse outcomes in patients with systemic hypertension,[19] pulmonary arterial hypertension,[17,18] and HF with either preserved or reduced LVEF.[12–16] The invasively measured TASV/RVSP ratio has been associated with symptoms, hemodynamic compromise, and outcomes in patients with HF and preserved LVEF, including patients undergoing transcatheter aortic valve replacement.[20–24] Our study further validates these studies, and emphasizes that RV-PA coupling, as measured noninvasively using the TASV/RVSP ratio, is an important prognostic marker, even among critically ill CICU patients. Indeed, we found that the TASV/RVSP ratio, as measured by Doppler TTE, was among the strongest predictors of 1-year mortality among hospital survivors; the idea that a single Doppler TTE measurement during hospitalization can prognosticate long-term, even among hospital survivors, is remarkable and warrants prospective examination for validation. Notably, most studies

examining RV-PA coupling using either the TAPSE/RVSP or the TASV/RVSP ratio have included primarily patients with chronic PH and RV dysfunction rather than patients with acute RV strain attributable to pulmonary embolism or acute RV injury attributable to RV infarction in whom PA pressures may be reduced because of low RV stroke volume. Although not previously examined, it is likely that disease chronicity can influence not only the measured TASV/RVSP ratio, but also the association of RV-PA coupling with clinical outcomes.

The robust associations between impaired RV-PA coupling (ie, a low TASV/RVSP ratio) and higher mortality suggest that interventions to improve coupling may improve outcomes. Such therapeutic interventions might include treatments to reduce RA and PA pressure using either diuretics or interventions that act directly on the pulmonary vasculature.[1–4] Fluid removal can improve PA pressures and RV-PA coupling through a reduction in filling pressures, which can decrease right heart dilation and alleviate pericardial restraint.[1–4,39] Alternatively, severely decompensated patients may benefit from short-term inotropic support to enhance RV-PA coupling during the short-term and allow for recovery from acute insults.[1–4] Notably, reduced RV-PA coupling correlated with impaired LV systolic and diastolic dysfunction, emphasizing the importance of right-sided heart disease among patients with left-sided heart failure and suggesting the need to optimize biventricular function in many patients.[40] Serial measurement of the TASV/RVSP ratio using bedside Doppler TTE could help to understand the effects of treatments on RV-PA coupling, and potentially to monitor for adverse heart-lung interactions in mechanically ventilated patients. Further study is required to examine whether currently available therapies for PH and RV failure can improve RV-PA coupling and outcomes in CICU patients.

Limitations

This analysis carries the same limitations common to all retrospective observational studies, and cannot infer causation. Missing TTE data could have influenced the results and introduced bias, particularly considering that fewer than half of patients with a TTE had data available for calculating the TASV/RVSP ratio and that the baseline characteristics and outcomes differed significantly between included and excluded patients. Poor imaging windows in sicker patients could have prevented complete data acquisition, leading to bias, and TTE data were obtained without the objectives of this study in mind. It is likely that TASV and TAPSE were preferentially measured among patients with abnormal RV structure or function, and RVSP can only be estimated among patients with sufficient TR to acquire a Doppler signal; our institution measures TASV more frequently than TAPSE, limiting our ability to compare these 2 related measures robustly. Serial TTE data were not available, preventing us from assessing changes in RV-PA coupling over time. Likewise, we did not have invasive hemodynamic data to correlate with and corroborate measured Doppler TTE hemodynamic values, nor did we have data on symptoms, physical examination, imaging, or ECG, which limits our ability to draw firm inferences. In addition, we were not able to determine the acuity or specific cause of PH and RV dysfunction, precluding us from determining whether abnormal values of TASV/RVSP reflected acute or chronic pathological features. A potential limitation of the TASV/RVSP ratio is that echocardiographic estimation of RAP has demonstrated only modest correlations with invasive measurements in patients receiving positive-pressure ventilation, and echocardiography may underestimate RAP and PA pressures when RAP is high.[41,42] However, the simplified TASV/TR velocity ratio, which does not depend on RAP, had an AUC for hospital mortality that was only modestly lower than the TASV/RVSP ratio. We could not determine the therapies that patients were receiving at the time of TTE (such as vasoactive drugs), preventing us from inferring the relationship between medical treatments and RV-PA coupling. Given the numerous potential confounders that can affect late mortality after hospitalization in CICU patients, our 1-year mortality analysis should be considered exploratory and interpreted with caution.

CONCLUSIONS

In the largest human study of RV-PA coupling in an unselected CICU cohort, our findings suggest a robust inverse association between TASV/RVSP ratio and mortality risk during and following hospitalization. This study emphasizes the potential usefulness of Doppler TTE measurements for characterizing the prognostically important hemodynamic abnormalities that are common in CICU patients. Future prospective studies will be needed to confirm the association between the TASV/RVSP ratio and outcomes in CICU patients and to determine whether its prognostic value is influenced by cause and response to short-term therapy, to provide further insights into how this easily obtained bedside imaging biomarker can be integrated into clinical practice.

ARTICLE INFORMATION

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Affiliations

From the Department of Cardiovascular Medicine (J.C.J., N.S.A., Y.N.R., B.M.W., J.K.O., B.A.B.)Division of Pulmonary and Critical Care Medicine (J.C.J., Y.N.R.) and Department of Health Sciences Research, Mayo Clinic Rochester, Rochester, MN (D.H.M.).

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None.

Supplementary Material

Tables S1–S2
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Measured and derived echocardiographic variables of interest.

Variable
Systolic blood pressure
Diastolic blood pressure
Mean blood pressure
Pulse pressure
Heart rate
Shock index
Heart rhythm (sinus rhythm or atrial fibrillation)
Left ventricular ejection fraction (LVEF)
Wall motion score index
Left ventricular outflow tract (LVOT) peak velocity
LVOT velocity-time integral (VTI)
Stroke volume (SV)
Stroke volume index (SVI)
Cardiac output (CO)
Cardiac index (CI)
Lateral mitral annulus peak systolic tissue Doppler (s') velocity
Early mitral diastolic (E) velocity
Mitral atrial diastolic (A) velocity
Mitral E/A velocity ratio
Medial mitral annulus early diastolic tissue Doppler (e') velocity
Mitral E/e' velocity ratio
Right atrial pressure (RAP)
Tricuspid regurgitation (TR) peak systolic velocity
Tricuspid annulus peak systolic velocity (TASV)
Tricuspid annular plane systolic excursion (TAPSE)

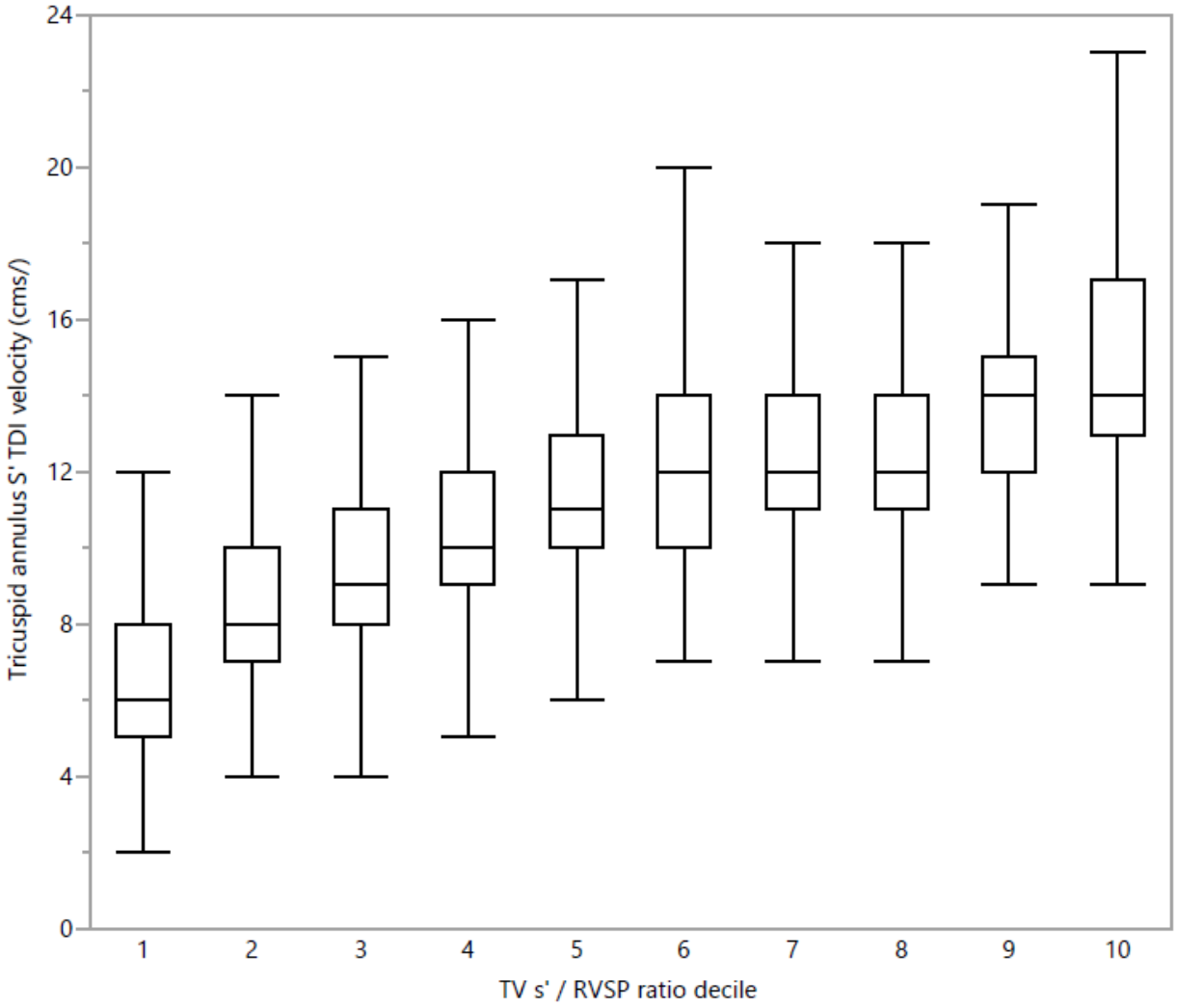
Table S2. Formulas used for echocardiographic hemodynamic parameters, using data from the time of the echocardiogram.

Echocardiographic parameter	**Formula**
Mean arterial pressure (MAP)	[SBP + (2 * DBP)] / 3
Stroke volume (SV)	$(\pi/4)$ * LVOT VTI * (LVOT diameter)^2
Stroke volume index (SVI)	SV / BSA
Cardiac output (CO)	SV * HR (at time of LVOT VTI acquisition)
Cardiac index (CI)	CO / BSA = SVI * HR
Cardiac power output (CPO)	(CO * MAP) / 451
Pressure-adjusted heart rate (PAHR)	(HR * RAP) / MAP
Right ventricular systolic pressure (RVSP)	RAP + [4 * (peak TR velocity)^2]
TASV/RVSP ratio	TASV / RVSP
TAPSE/RVSP ratio	TAPSE / RVSP
TASV/TR velocity ratio	TASV/TR velocity

BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; LVOT, left ventricular outflow tract; RAP, right atrial pressure; SBP, systolic blood pressure; VTI, velocity-time integral.

Figure S1. Tricuspid annulus systolic velocity (TV s') by tissue Doppler imaging (TDI) (A) and estimated right ventricular systolic pressure (RVSP) by continuous-wave Doppler (B) as a function of TV s' to RVSP ratio decile.

A



B

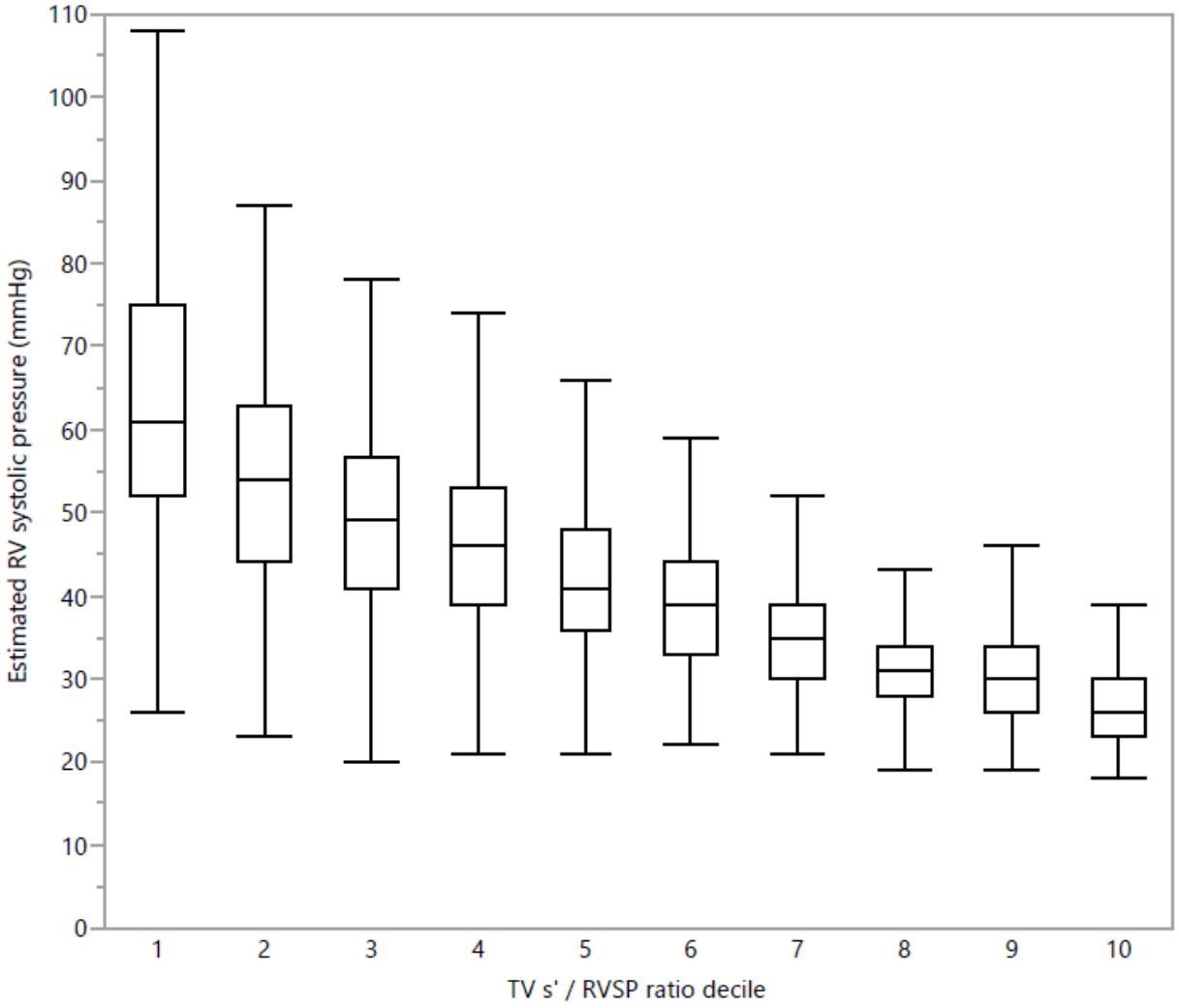

Estimated RV systolic pressure (mmHg)
110
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
TV s' / RVSP ratio decile

Figure S2. Tricuspid annular plane systolic excursion (TAPSE) to right ventricular systolic pressure (RVSP) ratio as a function of tricuspid annulus systolic velocity (TASV) to RVSP ratio decile.

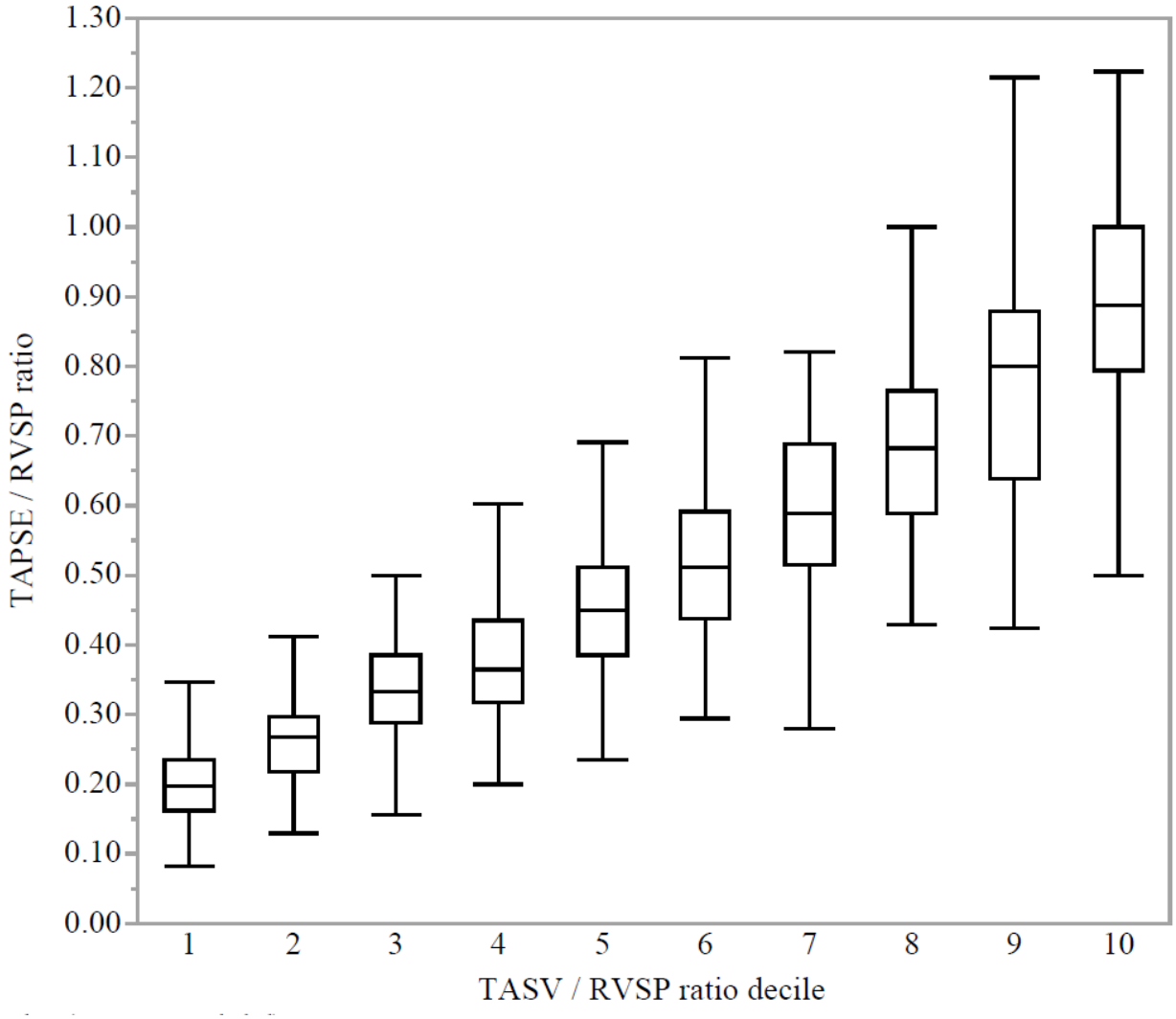


Figure S3. CICU and hospital mortality as a function of TASV/RVSP ratio quintile. A higher TASV/RVSP ratio quintile reflects better RV-PA coupling, and each higher TASV/RVSP quintile was associated with lower hospital mortality (unadjusted OR 0.560 per each higher quintile, 95% CI 0.507-0.617, p <0.001). All p <0.001 for trends across