Association between Right-Sided Cardiac Function and Ultrasound-based Pulmonary Congestion on Acutely Decompensated Heart Failure: Findings from A Pooled Analysis of 4 Cohort Studies

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Abstract

Background

Right ventricular (RV) dysfunction and RV-pulmonary artery (PA) uncoupling are associated with the development of pulmonary congestion during exercise. However, there is limited information regarding the association between these right-sided cardiac parameters and pulmonary congestion in acutely decompensated heart failure (HF).

Methods

We performed an individual patient meta-analysis from four cohort studies of hospitalized patients with HF who had available lung ultrasound (B-lines) data on admission and/or at discharge. RV function was assessed by tricuspid annular plane systolic excursion (TAPSE), RV-PA coupling was defined as the ratio of TAPSE to PA systolic pressure (PASP).

Results

Admission and discharge cohort included 319 patients (75.8±10.1 years, 46% women) and 221 patients (77.9±9.0 years, 47% women), respectively. Overall, higher TAPSE was associated with higher ejection fraction, lower PASP, b-type natriuretic peptide and B-line counts. By multivariable analysis, worse RV function or RV-PA coupling were associated with higher B-line counts on admission and at discharge, and with a less reduction in B-line counts from admission to discharge. Higher B-line counts at discharge were associated with a higher risk of the composite of all-cause mortality and/or HF re-hospitalization [adjusted-HR=1.13 (1.09-1.16), p<0.001]. Furthermore, the absolute risk increase related to high B-line counts at discharge was higher in patients with lower TAPSE.

Conclusions

In patients with acutely decompensated HF, impaired RV function and RV-PA coupling were associated with severe pulmonary congestion on admission, and less resolution of pulmonary congestion during hospital stay. Worse prognosis related to residual pulmonary congestion was enhanced in patients with RV dysfunction.

Keywords: Pulmonary congestion; Lung ultrasound; Right heart; Hemodynamics; Acutely decompensated heart failure; Diastolic heart failure; Cardiac edema.

Introduction

Increased fluid filtration due to elevated pulmonary capillary pressure leads to an increase in extravascular lung water, and pulmonary congestion in patients with heart failure (HF) [1, 2]. Pulmonary congestion is one of the main causes leading to urgent HF hospitalization and subsequent poor patient outcomes [3, 4]. Lung ultrasound (LUS) detects pulmonary congestion with high sensitivity and specificity, which is independently associated with worse prognosis in patients with chronic HF or acutely decompensated HF (ADHF) [5-11].

Right ventricular (RV) function and RV-pulmonary artery (PA) coupling (which is a measure of the balance between RV function and the properties of the pulmonary circulation) might be both impaired in HF, regardless of their ejection fraction (EF) [3, 12], and are associated with worse prognosis [13-15]. A recent report showed that these abnormalities are associated with the development of pulmonary congestion during exercise in patients with HF and preserved EF [16]. This finding was inconsistent with classical perception suggesting that RV output exceeding left ventricular (LV) output contributed to the development of pulmonary congestion [17, 18]. In addition, there may be a bi-directional relationship between pulmonary congestion and RV function since perivascular congestion or associated atelectasis may directly compress the pulmonary vasculature and increase RV afterload [19-21].

In the specific context of patients with ADHF, it remains unclear about the underlying interaction between right-sided cardiac function and pulmonary congestion. In particular, whether RV function and/or RV-PA coupling is associated with a higher degree of pulmonary congestion (i.e. either admission, discharge, or change from admission to discharge) is scarcely studied. In addition, whether the prognostic impact of pulmonary congestion is modified by RV dysfunction/RV-PA uncoupling is yet to be determined.

The aims of the present study are to investigate the association of RV function or RV-PA coupling with pulmonary congestion assessed by LUS (admission, discharge and change from admission to discharge), and to explore whether the association of pulmonary congestion with the risk of clinical events is influenced by RV function or RV-PA coupling.

Methods

Pooled Patient Population

The current pooled study was performed as a patient-level meta-analysis combining datasets from four independent cohort studies of patients who survived their initial hospital stay.

The Nancy cohort study (admission); The Nancy cohort study included patients who were hospitalized for ADHF at the Institut Lorrain du Coeur et des Vaisseaux in France from April 2014 to August 2015, as previously reported[6]. Physical examination and laboratory data were assessed on admission. LUS was performed once, within the first 3 days following admission.

The Perugia cohort study (discharge); The Perugia cohort study included patients who were hospitalized for ADHF at the Division of Cardiologia e Fisiopatologia Cardiovascolare in Perugia from April 2014 to October 2014, as previously reported[5, 6]. Physical examination, laboratory data and LUS were assessed at discharge.

The Pisa cohort study (admission); The Pisa cohort study included patients who were hospitalized for ADHF in the Cardiology Department in Pisa from October 2004 to October 2008, as previously published [9]. Physical examination, laboratory data and LUS were assessed on admission.

The Siena cohort study (admission and discharge); The Siena cohort study included patients with ADHF in sinus rhythm, as previously shown [8]. All patients underwent echocardiography within 12 hours from admission. Clinical, biological and LUS data were assessed both on admission, and at discharge.

For this pooled analysis, we included patients for whom data on baseline tricuspid annular plane systolic excursion (TAPSE) and LUS were available. Other main exclusion criteria in the present merged dataset were; (i) poor acoustic window, (ii) pulmonary fibrosis, previous pneumectomy or lobectomy, pulmonary cancer or metastases, breast prosthesis; (iii) acute myocardial infarction, (iv) cardiogenic shock and (v) severe sepsis. Each cohort study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committees.

Echocardiography

Left ventricular EF (LVEF) was measured using the modified biplane Simpson's method. Diastolic function was assessed from the pattern of mitral inflow by pulsed-wave Doppler. Mitral annular early diastolic velocity (e') was assessed at the septal and lateral sites of the mitral annulus using tissue Doppler imaging. E/A ratio, e' mean and E/e' mean ratio were calculated [22]. Inferior vena cava (IVC) and TAPSE measurements were obtained as recommended [23]. Pulmonary arterial systolic pressure (PASP) was estimated using tricuspid velocity and inferior vena cava compliance and diameter according to recent guidelines [23]. Patients were classified according to LVEF, reduced EF (LVEF<40%) and mid-range/preserved EF (LVEF≥40%).

Lung Ultrasound

Lung ultrasound was performed at each site by trained investigators, according to standardized protocols: eight LUS zones were analyzed for each patient, and B-lines were defined as previously described[24]. A phased-array probe was used with parallel orientation to the ribs (transverse approach). For each scanning site, the lung was observed for at least one complete respiratory cycle. When B-lines were clearly distinguishable, they were counted one by one; when they were confluent the percentage of the white screen compared with the black screen below the pleural line was considered, and then divided by 10 [24]. The maximum number of B-line was counted for each zone and the sum of all 8 zones was considered as total number of B-line counts. In the Pisa, Nancy and Perugia cohort studies, we also calculated B-line counts in 28-point method as previously reported [25]. Inter- and intra-rater variability for this imaging technique in each laboratory have previously been presented [5, 6, 8, 9].

Study Outcomes

The primary outcome was the composite of all-cause mortality and/or HF re-hospitalization. All patients were systematically followed after discharge in each institution. The median of follow-up periods of

each cohort study was 90.0 [64.3–71.3] days in the Nancy study, 90.0 [61.0–90.0] days in the Perugia study, 416.0 [233.0–923.0] days in the Pisa study, and 180.0 [98.0–180.0] days in the Siena study.

Statistical Analysis

We integrated patient-level datasets from admission data (Nancy, Pisa and Siena cohort studies) and discharge data (Perugia and Siena cohort studies). Categorical variables therefore are expressed as frequencies (percentages) and continuous variables as adjusted means (25th and 75th percentiles) after adjustment for cohort-difference. Patients were divided into three groups according to the tertiles of TAPSE. Given the recent emphasis on the usefulness of TAPSE/PASP ratio to evaluate right ventriculoarterial coupling[26], we also divided our cohort according to TAPSE/PASP ratio. Comparisons of demographic, clinical, biological, echocardiographic and LUS parameters across TAPSE (or TAPSE/PASP ratio) tertiles were analyzed using logistic regression analysis for categorical variables and linear regression analysis for continuous variables after adjustment for cohort-difference.

Linear regression analyses were used to investigate the association of TAPSE and TAPSE/PASP ratio with B-lines score on admission and discharge. In the Siena cohort study, the association between TAPSE, TAPSE/PASP ratio and B-line count change from admission to discharge was investigated. Changes in B-line count was considered as absolute change (admission B-line count – discharge B-line count) and relative change [(admission B-line count – discharge B-line count)/admission B-line count].

Time-to-event comparisons were analyzed using log-rank test and Cox proportional hazards models. Survival probabilities were estimated using the Kaplan-Meier method and plotted as survival curves with cohort study-specific tertiles of B-line counts. Cox proportional-hazards models were then used to obtain unadjusted and covariate adjusted hazard ratios (HRs). The covariates used for adjustment included cohort-difference, age, sex, a history of ischemic heart disease, atrial fibrillation, LVEF, systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR, calculated by the Chronic Kidney Disease Epidemiology Collaboration formula [27]) and IVC diameter. The absolute risk differences at 90 days, between each of high and intermediate B-line count groups and the low B-line count group, were also assessed.

Statistical analyses were performed using R (R Development Core Team, Vienna, Austria). Imputation was not performed. A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

In the admission cohort (N=319), mean age was 75.8±10.1 years, 45.5% were women and mean LVEF was 39.2±13.9% and tertile TAPSE distribution was <16mm in Tertile I, 16 to 20mm in Tertile II, and >20mm in Tertile III. In the discharge cohort (N=221), mean age was 77.9±9.0 years, 46.6% were women and mean LVEF was 41.5±13.3% and tertile TAPSE distribution was <17mm in Tertile I, 17 to 20mm in Tertile II, and >20mm in Tertile III.

Overall, patients with higher TAPSE had higher EF, lower PASP, smaller IVC diameter, lower b-type natriuretic peptide (BNP) and B-line counts (all p-value<0.05) (**Table 1**). In the admission cohort, patients with higher TAPSE had less frequent ischemic heart disease and higher SBP, whereas patients with higher TAPSE had less severe congestion in the discharge cohort.

Patient characteristics according to the tertiles of TAPSE/PASP ratio is shown in **Supplementary table 2**. We observed that clinical and echocardiographic features associated with TAPSE/PASP ratio were similar to those associated with TAPSE.

The associations of TAPSE and TAPSE/PASP ratio with B-line counts across LVEF strata in the admission and discharge cohort are presented in **Supplementary table 3**. Patients with higher TAPSE/PASP ratio had less B-lines on admission and at discharge across LVEF strata.

Associations of RV Function and RV-PA Coupling with B-line Counts at Admission, Discharge and Change from Admission to Discharge

In the multivariable model including cohort-difference, age, sex, ischemic heart disease, LVEF, SBP, sodium and eGFR, patients with lower TAPSE and TAPSE/PASP ratio had significantly higher B-line counts on admission (all p-value<0.01) (**Table 2**). After adjusting for the aforementioned variables plus E/e' and

BNP, lower TAPSE/PASP ratio remained significantly associated with higher B-line counts on admission. Similarly, we observed that lower TAPSE or TAPSE/PASP ratio were associated with higher discharge B-line counts (all p-value<0.05). Furthermore, after adjustment for cohort, E/e' and BNP (without adjusting for other factors), TAPSE/PASP ratio remained significantly associated with B-line counts (**Supplementary table 4**).

The association of TAPSE or TAPSE/PASP ratio with an absolute or a relative change in B-line count during hospital stay is presented in **Table 3**. After adjusting for potential confounders, higher TAPSE and TAPSE/PASP ratio were significantly associated with a greater reduction in B-line counts (all p-value<0.05).

Survival Analysis

The primary outcome occurred in 34.2% (N=109) and 35.7% (N=79) of patients in the admission cohort and discharge cohort, respectively. Higher B-line counts on admission were not associated with the primary outcome, whereas the primary outcome occurred more frequently in patients with greater B-line counts at discharge (**Figure 1**). In the multivariable model, higher B-line counts at discharge remained significantly associated with a higher risk of the primary outcome [per 1 increase in B-line count; adjusted-HR (95%CI)=1.13 (1.09-1.16), p<0.001] (**Figure 2**).

With regard to the primary outcome, we found no significant interaction between B-line count both on admission and at discharge and tertiles of TAPSE or TAPSE/PASP ratio (all $p_{interaction}$>0.10) (**Figure 2**). However, at 90 days, the absolute risk increase related to high B-line counts at discharge (Tertile III vs Tertile I in B-line counts) was higher in the low- (53.1%) and intermediate TAPSE group (53.5%) vs high TAPSE group (18.7%) (**Central Illustration & Supplementary figure 1**).

Discussion

In the current study, we assessed the relationship between RV dysfunction/RV-PA uncoupling and pulmonary congestion assessed by LUS in patients with ADHF. We found that impairments in RV systolic function and RV-PA coupling were associated with a higher number of B-line, both on admission and at discharge, and that these RV functional abnormalities were also associated with persistent pulmonary congestion with an impaired reduction in B-line count from admission to discharge. The number of B-lines at discharge, but not at admission, was a powerful predictor of adverse outcome, irrespectively of RV dysfunction or RV-PA uncoupling. These findings highlight the clinical importance of assessing right heart function, which may be an important factor favoring the development and persistence of pulmonary congestion in HF independent of left-sided cardiac function.

The Interplay of Right-sided Hemodynamics and Pulmonary Congestion in Patients with Acutely Decompensated Heart Failure

Elevation in left-sided filling pressure leads to retrograde increased pulmonary capillary pressure/central venous pressure, with consequent impairments in RV function/RV-PA coupling [28]. Therefore, there has been a traditional focus on the left heart in determining pulmonary edema. However, RV dysfunction and RV-PA uncoupling have recently been shown to be associated with the development of pulmonary congestion during exercise in patients with HF and preserved EF [16]. This association could be the result of decreased ability of lymphatics to remove fluid from the interstitial tissue in lungs to the subclavian venous system in patients with increased right atrial pressure [29], related to impairment in RV function/RV-PA coupling. This result suggests that RV dysfunction is a factor favoring pulmonary congestion. Collectively, these findings challenge the classical view, which suggests that pulmonary congestion is the result of RV output exceeding LV output [17, 18].

Indeed, in the current pooled analysis, we observed that patients with impaired RV function and RV-PA uncoupling were associated with increased lung water independently of left-sided filling pressure as assessed by BNP and E/e'. Prior reports showed that decreased RV fractional area correlated with increased pulmonary congestion in ambulatory patients with HF [21, 30]. In our study, impaired RV-PA coupling was

associated with increased B-line counts across LVEF strata. This is in line with the similar impairments in right-sided hemodynamic parameters reported in ADHF patients with preserved or reduced EF [3]. Taken together, these observations suggest that independent of the severity of left-sided cardiac function, the development of pulmonary congestion is also dependent on the degree of RV dysfunction which may be related to its impact on impeding lymphatic drainage from the lung[16, 31]. It has also been suggested that the relationship between lung water and RV function may be bidirectional since the accumulated extravascular lung water may compress extra-alveolar arterioles and increase right heart afterload [32] as suggested by animal studies [19], which could in turn result in impaired RV function. Interestingly, in the present study, TAPSE was not associated with E/e', but was significantly associated with LVEF, which is consistent with previous reports [33, 34]. This result may suggest a concomitant progression of biventricular dysfunction rather than RV afterload due to elevated LV filling pressure [35].

In the pooled data reported herein, we found that only discharge pulmonary congestion (as assessed with B-lines) was associated with a higher risk of mortality and HF re-hospitalization, which is consistent with previous reports [7, 36]. Interestingly, we observed no statistical interaction on a relative scale between RV function/RV-PA coupling and B-line counts with regard to the primary outcome. However, as patients with RV dysfunction are at a higher risk for outcomes, a similar association on a relative scale may translate into quite different associations on an absolute scale [37, 38]. Indeed, our further results showed that absolute risk increase associated with higher B-line counts was enhanced in patients with more severe RV dysfunction. These results suggested greater prognostic impact of severe residual pulmonary congestion in patients with depressed RV function, and prognostic importance of assessing RV function in patients with residual pulmonary congestion.

RV Dysfunction and RV-PA Uncoupling Predicted Changes in Pulmonary Congestion

In patients with ADHF, resolution of pulmonary congestion is one of the main goals to decide the timing of discharge [3]. Diabetes, body size, blood pressure and renal impairment were reported to be independent predictors of residual congestion and/or diuretic resistance [39, 40]. In the current study, independent of clinical confounders and admission pulmonary congestion, impaired RV function at baseline was associated with impaired clearance of pulmonary congestion from admission to discharge. The

pathophysiological mechanisms behind this association are unclear, and cannot be answered by the present study, but a number of possibilities exist. The association may be explained by impaired lymphatic clearance from the lungs with elevated subclavian venous pressures from abnormal RV-PA coupling[16, 31], increased RV-afterload from lung edema compressing the vasculature contributing to RV dysfunction[19-21]. Furthermore, renal venous congestion in patients with RV dysfunction might lead to a poor diuretic response and subsequent residual pulmonary congestion [32, 41]. These results may encourage clinicians select more aggressive diuretic therapy in patients with impaired RV function who are more likely to experience residual pulmonary congestion.

Clinical Perspectives

Increased left-sided filling pressure leads to pulmonary congestion (interstitial and alveolar edema) and symptoms [42, 43]. While symptomatic congestion may successfully resolve with decongestion therapy, subclinical residual pulmonary congestion may persist at discharge. Our results suggested that RV dysfunction and/or RV-PA uncoupling may play a pivotal role in both the onset and resolution of pulmonary congestion. A better understanding of the underlying relationship between lung congestion and right-sided hemodynamics may help clinicians optimize decongestive therapy. In a way, our results support that RV dysfunction may directly contribute to pulmonary edema contrary to the traditionally dominant perceived role of the left ventricle.

Importantly, our results also further emphasize the key importance of ultrasound-based residual pulmonary congestion [5]. In our study, the prognostic performance of discharge congestion was more important than the one of admission congestion. These results are in line with recent reports drawing similar conclusions using radiographic pulmonary congestion[36] or estimated plasma volume[44]. A large array of data suggest that discharge congestion has more critical prognostic implications than admission congestion.

Limitations

Our study has several limitations. First, although this is a patient-level pooled analysis we cannot infer causality nor exclude residual confounders. Second, individual cohorts had some differences in variables'

measurements and patients' selection. Third, Echocardiography and LUS were assessed by experienced practitioners in each institution, although good reproducibility of B-line counts across different cohort studies have been reported [5, 6, 8, 9]. B-line counts were different depending on cohort studies, possibly because of the different patient settings of the four cohort studies. Fourth, hemodynamic data was not available. In addition, we had no data regarding mitral regurgitation and left atrial volume in this meta-analysis. Fifth, in the Nancy cohort, patients underwent LUS once within 3 days from their admission; therefore, prior administration of diuretic therapy may have influenced B-line counts in these patients. Lastly, we had no available information about other right-sided cardiac parameters (i.e., RV systolic tissue velocity or fractional area change) however, TAPSE is a well validated marker of RV function.

Patients underwent only one research echocardiography on admission. The absence of discharge echocardiography limited our understanding of the association between echo data and residual pulmonary congestion at discharge. In addition, we were unable to assess changes in right ventricular, but also left ventricular and atrial, size and function between admission and discharge. It might be possible that inability to correct LV systolic function or filling pressure might have had an impact on the residual amount of B-lines at discharge. More studies are needed to clarify these associations.

Conclusion

Impaired RV function and RV-PA uncoupling are associated with more severe pulmonary congestion and less resolution of pulmonary congestion during hospital stay in patients admitted for acutely decompensated HF, regardless of LVEF. Worse prognosis of residual pulmonary congestion was enhanced in patients with severe RV dysfunction. These data support the clinical importance of right-sided cardiac function which may be a relevant factor favoring the development and persistence of pulmonary congestion, and influencing worse prognosis of residual pulmonary congestion. Our results also emphasize the key importance of assessing pulmonary residual congestion in patients with acutely decompensated HF.

Conflict of interests

NG received honoraria from Novartis and Boehringer. NG and PR are supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project Lorraine Université d'Excellence GEENAGE (ANR-15-IDEX-04-LUE) programs, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP. PR reports grants and personal fees from AstraZeneca, Bayer, CVRx, Fresenius, and Novartis, personal fees from Grunenthal, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, Relypsa.

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Figure 1. Kaplan-Meier Survival Curves for the Composite of All-cause Death and/or Heart Failure Re-hospitalization according to the Cohort Study Specific Tertiles of B-line Counts

Figure 2. Associations of B-line Counts with the Composite of All-cause Mortality and/or Heart Failure Re-hospitalization according to TAPSE or TAPSE/PASP Ratio

AHR, adjusted hazard ratio; CI, confidence interval; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure

Central Illustration.

TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure.

Figure 1. Kaplan-Meier Survival Curves for the Composite of All-cause Death and/or Heart Failure Re-hospitalization according to the Cohort Study Specific Tertiles of B-line Counts

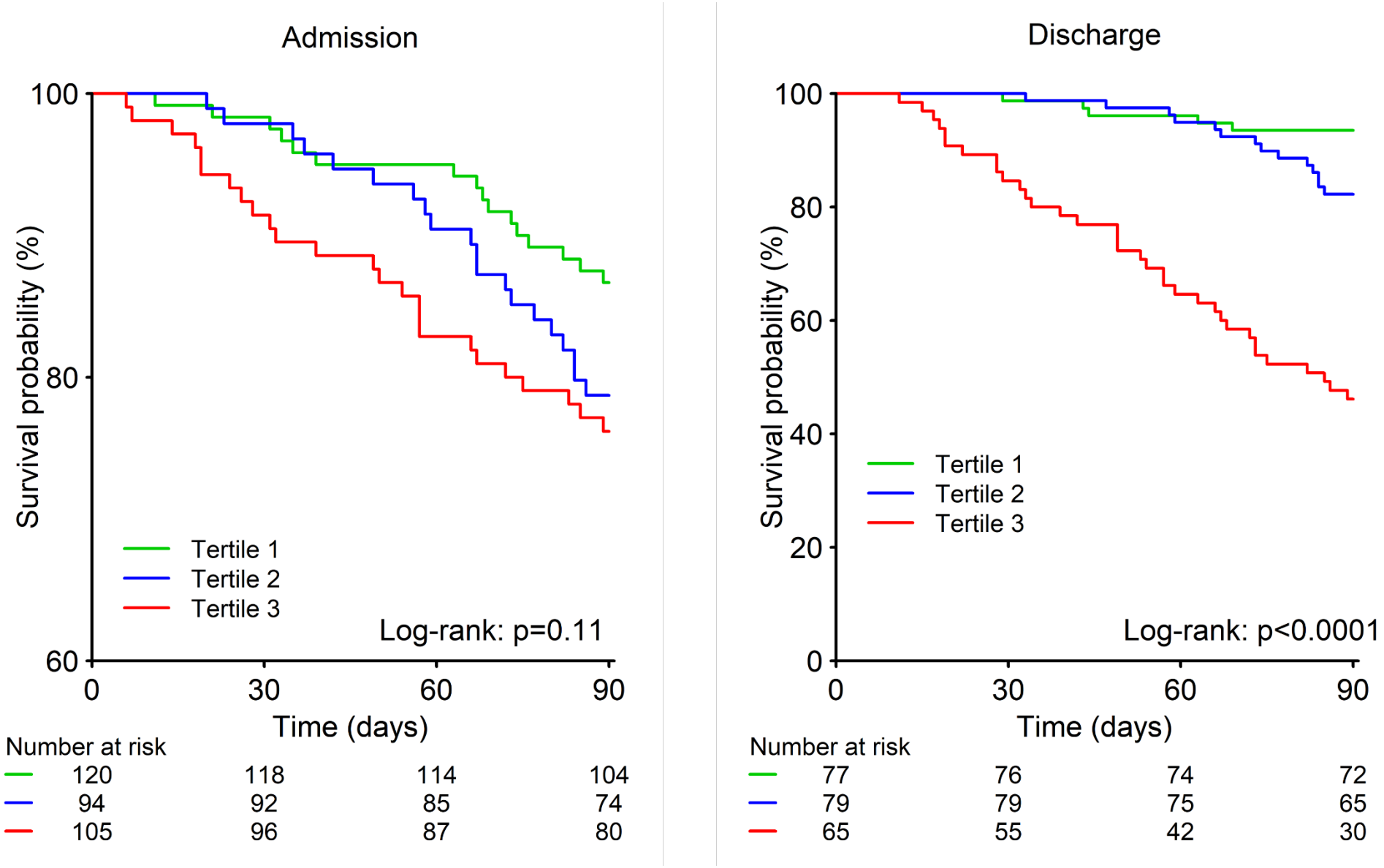
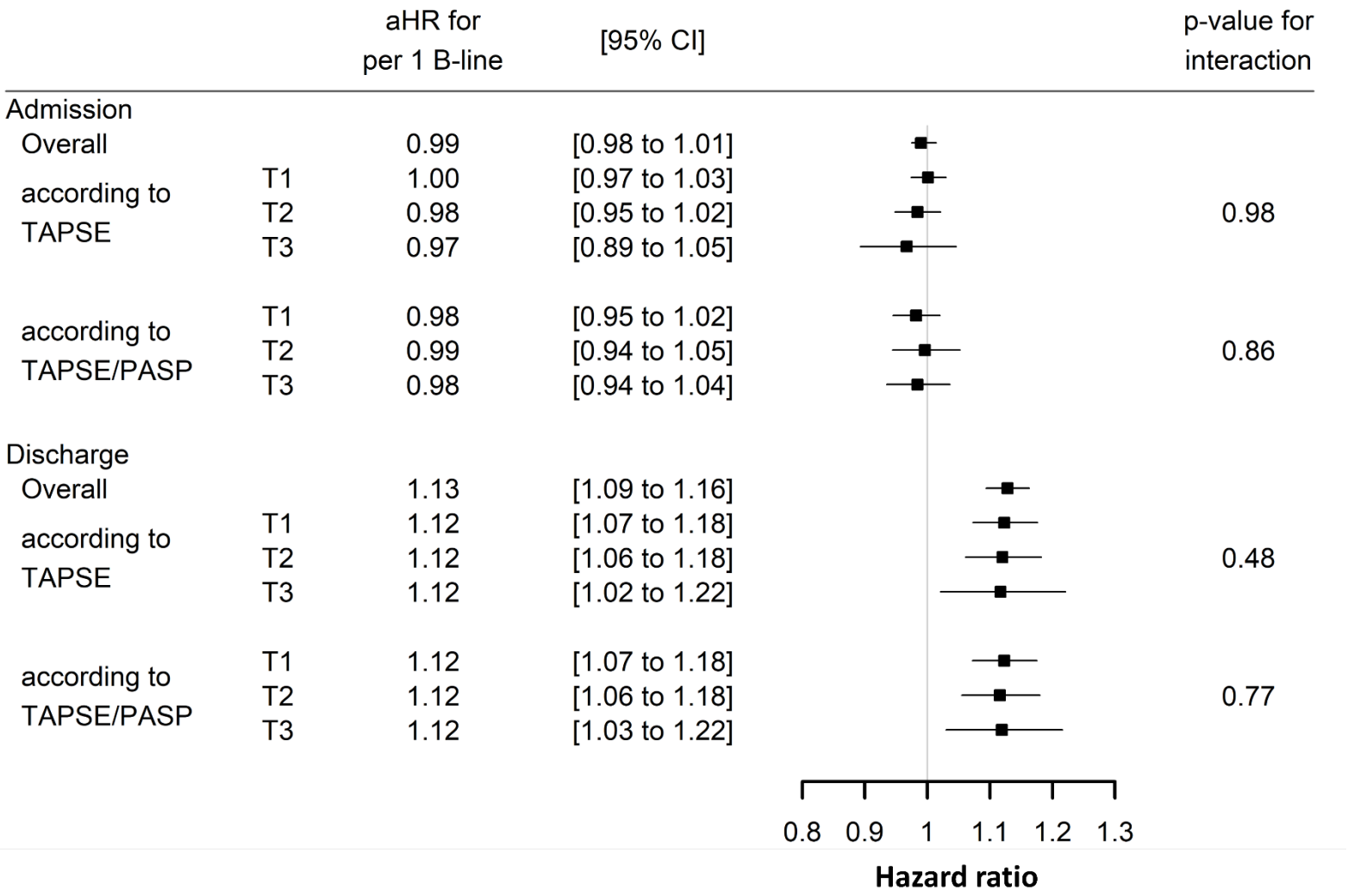
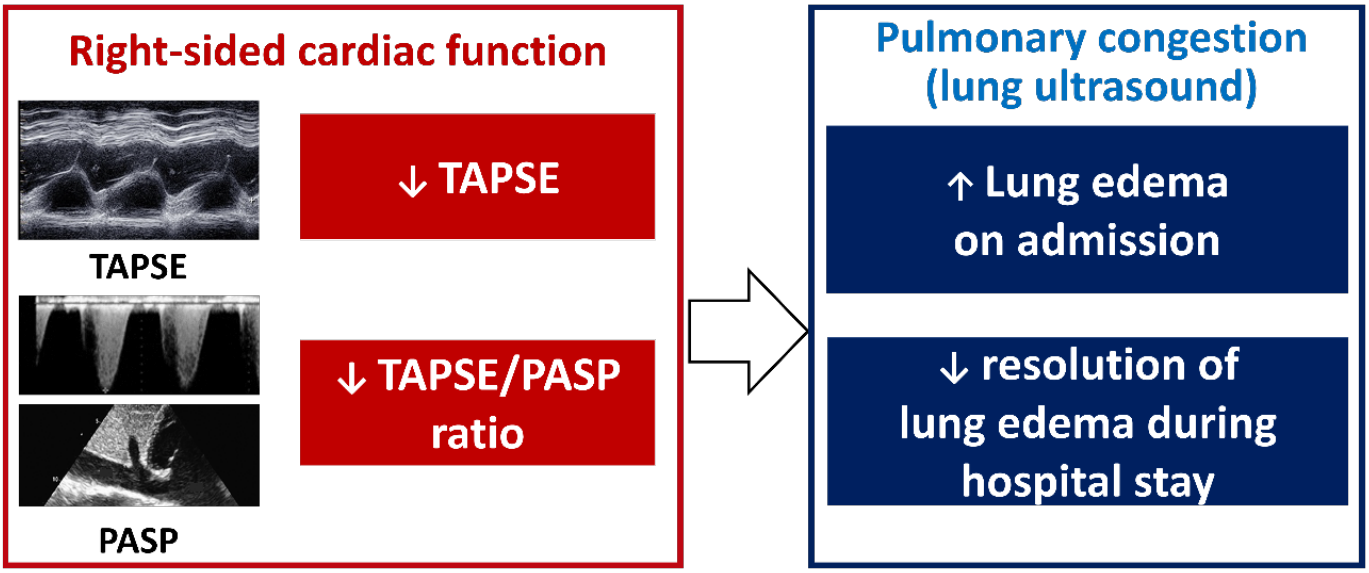


Figure 2. Associations of B-line Counts with the Composite of All-cause Mortality and/or Heart Failure Re-hospitalization according to TAPSE or TAPSE/PASP Ratio



Central Illustration



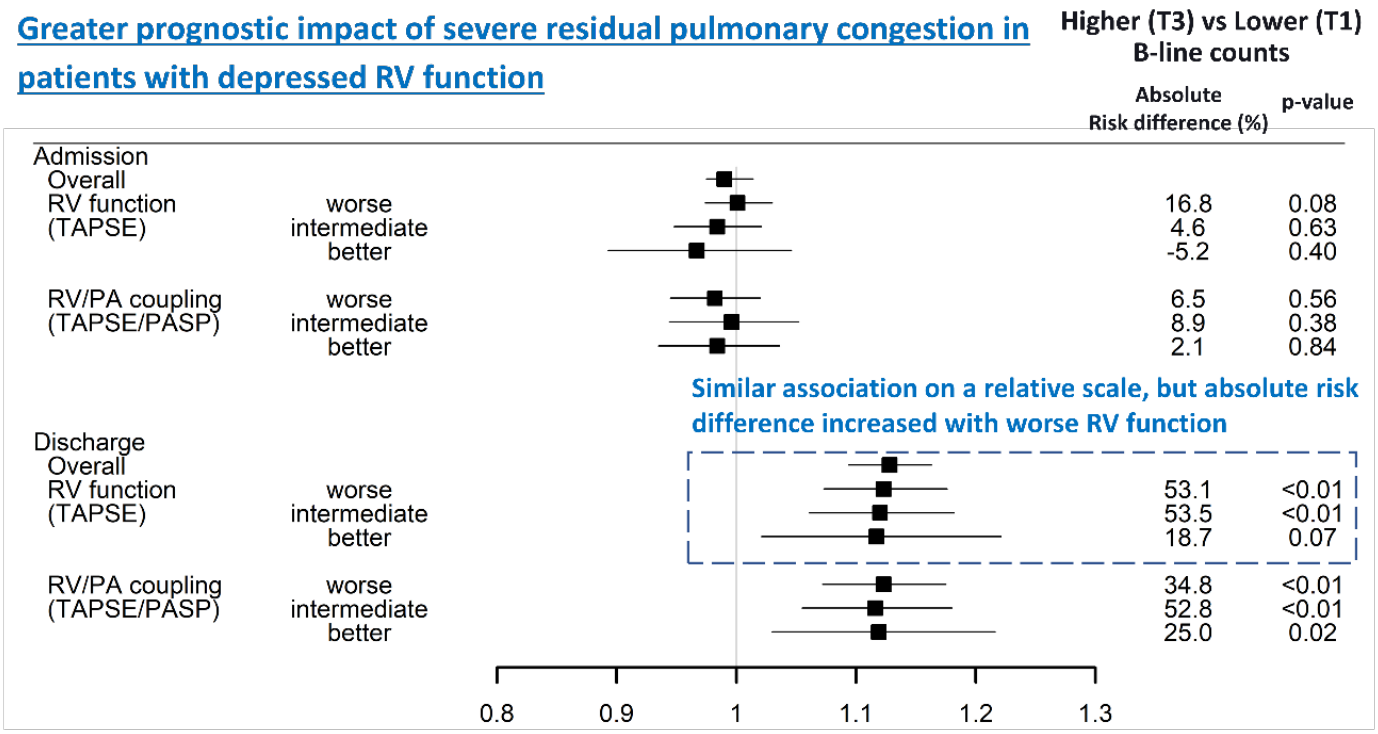


Table 1. Baseline Characteristics according to the Tertiles of TAPSE

Values are adjusted mean (95% confidence interval) and n (%). Linear regression or logistic regression was used to adjust for cohort difference.

TAPSE, tricuspid annular plane systolic excursion; BP, blood pressure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; BNP, brain type natriuretic peptide; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; IVC, inferior vena cava.

Table 2. Associations of Right Ventricular Function with B-lines at Admission and Discharge

Model 1; adjusted for cohort-difference

Model 2; adjusted for cohort difference, age, sex, ischemic heart disease, left ventricular ejection fraction, systolic blood pressure, sodium and estimated glomerular filtration rate.

Model 3; adjusted for cohort difference, age, sex, ischemic heart disease, left ventricular ejection fraction, systolic blood pressure, sodium, estimated glomerular filtration rate, E/e' ratio and brain natriuretic peptide transformed by natural logarithm.

TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure.

Table 3. Associations of Right Ventricular Function with B-lines Change from Admission to Discharge in Siena Cohort Study

B-lines change (absolute) model

Model 1; adjusted for baseline B-line counts

Model 2; adjusted for baseline B-line counts, age, sex, body mass index, diabetes, ischemic heart disease, left ventricular ejection fraction, systolic blood pressure and estimated glomerular filtration rate.

B-lines change (relative) model

Model 1; univariable model

Model 2; adjusted for age, sex, body mass index, diabetes, ischemic heart disease, left ventricular ejection fraction, systolic blood pressure and estimated glomerular filtration rate.

TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure.

Table 1. Baseline Characteristics according to the Tertiles of TAPSE

	TAPSE							
	Admission cohort (N=319)				Discharge cohort (N=221)			
	Low <16mm (N=115)	Intermediate 16-20mm (N=117)	High >20mm (N=87)	Adjusted p-value	Low <17mm (N=80)	Intermediate 17-20mm (N=71)	High >20mm (N=70)	Adjusted p-value
Age, yrs	74.5 (72.8-76.3)	75.4 (73.4-77.3)	73.6 (71.4-75.7)	0.39	76.2 (74.3-78.0)	76.6 (74.5-78.8)	75.3 (73.2-77.4)	0.63
Women, N (%)	45 (39.1 %)	53 (45.3 %)	47 (54.0 %)	0.10	32 (40.0 %)	33 (46.5 %)	38 (54.3 %)	0.46
Ischemic heart disease	63 (54.8 %)	43 (36.8 %)	27 (31.0 %)	**0.008**	30 (37.5 %)	25 (35.2 %)	25 (35.7 %)	0.88
Atrial fibrillation	36 (31.6 %)	18 (15.7 %)	5 (5.7 %)	**0.02**	16 (20.0 %)	7 (9.9 %)	4 (5.7 %)	0.44
Clinical profiles								
Systolic BP, mmHg	120.3 (115.8-124.7)	127.7 (123.1-132.4)	129.8 (124.5-135.2)	**0.004**	118.6 (115.0-122.2)	121.9 (117.8-126.0)	121.2 (117.0-125.3)	0.45
Heart rate, bpm	90.2 (87.1-93.4)	89.3 (86.0-92.6)	87.5 (83.7-91.3)	0.44	84.5 (82.5-86.5)	84.2 (81.9-86.5)	82.1 (79.8-84.4)	0.22
Leg edema, N (%)	64 (55.7 %)	52 (44.8 %)	45 (51.7 %)	0.09	16 (20.0 %)	17 (23.9 %)	5 (7.1 %)	**0.02**
Rales, N (%)	82 (71.3 %)	80 (69.0 %)	64 (73.6 %)	0.74	28 (35.0 %)	16 (22.5 %)	11 (15.7 %)	**0.04**
ACEi or ARB	101 (87.8 %)	94 (80.3 %)	69 (79.3 %)	0.08	61 (76.2 %)	58 (81.7 %)	57 (81.4 %)	0.99
Beta-blocker	52 (45.2 %)	47 (40.2 %)	38 (43.7 %)	0.49	44 (55.0 %)	41 (57.7 %)	38 (54.3 %)	0.87
Loop diuretics	110 (95.7 %)	90 (76.9 %)	73 (83.9 %)	**0.001**	74 (92.5 %)	52 (73.2 %)	60 (85.7 %)	**0.005**
Laboratory findings								
Hemoglobin, g/dl	12.6 (12.2-13.1)	12.3 (11.8-12.8)	12.1 (11.6-12.6)	0.27	12.5 (12.1-13.0)	12.1 (11.6-12.6)	12.0 (11.4-12.5)	0.22
Sodium, mmol/l	139.3 (136.3-142.3)	139.1 (135.5-142.7)	138.0 (134.3-141.7)	0.82	138.9 (138.0-139.8)	139.2 (138.1-140.2)	139.3 (138.2-140.3)	0.85
eGFR, ml/min/1.73m²	56.9 (52.0-61.7)	59.5 (54.2-64.9)	60.6 (54.5-66.7)	0.59	54.7 (50.1-59.4)	54.3 (49.0-59.6)	56.8 (51.5-62.1)	0.75
BNP, pg/ml	1511 (1313-1709)	1034 (812-1255)	912 (670-1155)	**<0.001**	1139 (967-1311	645 (449-842)	641 (443-838)	**0.001**
Echo parameters								
LVEF, %	33.9 (31.4-36.4)	41.1 (38.3-43.8)	41.3 (38.2-44.5)	**<0.001**	37.7 (34.8-40.6)	44.1 (40.7-47.4)	43.2 (39.9-46.6)	**0.008**
E/A ratio	1.64 (1.44-1.84)	1.49 (1.30-1.69)	1.19 (0.97-1.40)	**0.002**	1.81 (1.59-2.03)	1.75 (1.50-1.99)	1.49 (1.26-1.72)	0.07
E/e' ratio mean	15.7 (14.6-16.7)	16.5 (15.2-17.7)	15.5 (14.1-16.9)	0.42	17.6 (16.3-18.9)	17.2 (15.7-18.6)	15.9 (14.4-17.4)	0.19
TAPSE, mm	13.1 (12.7-13.5)	18.2 (17.8-18.7)	22.5 (22.0-23.0)	**<0.001**	14.8 (14.5-15.2)	18.9 (18.6-19.3)	22.6 (22.2-23.0)	**<0.001**
PASP, mmHg	51.9 (49.3-54.4)	49.6 (46.7-52.5)	43.4 (40.1-46.8)	**<0.001**	45.9 (43.3-48.5)	47.6 (44.6-50.6)	39.0 (36.0-42.0)	**<0.001**
IVC, mm	22.6 (21.9-23.3)	20.6 (19.8-21.4)	19.7 (18.8-20.6)	**<0.001**	22.2 (21.4-22.9)	20.7 (19.9-21.6)	20.0 (19.2-20.9)	**<0.001**
TAPSE/PASP, mm/mmHg	0.27 (0.24-0.29)	0.40 (0.37-0.42)	0.57 (0.53-0.60)	**<0.001**	0.36 (0.32-0.39)	0.43 (0.39-0.47)	0.63 (0.59-0.67)	**<0.001**
B-line counts	23.1 (21.2-25.0)	20.8 (18.7-22.9)	18.4 (16.0-20.8)	**0.008**	15.6 (13.9-17.3)	13.1 (11.1-15.0)	11.1 (9.1-13.1)	**0.003**

Table 2. Associations of Right Ventricular Function with B-lines at Admission and Discharge

B-lines at admission, per 1		Model 1			Model 2			Model 3		
		beta	**95% CI**	**p-value**	**beta**	**95% CI**	**p-value**	**beta**	**95% CI**	**p-value**
TAPSE continuous (per 1mm)		-0.45	-0.72 to -0.18	**0.001**	-0.33	-0.64 to -0.01	**0.04**	-0.19	-0.48 to 0.10	0.19
TAPSE tertiles	**High**		(reference)			(reference)			(reference)	
	Intermediate	2.39	-0.47 to 5.25	0.10	1.27	-1.51 to 4.05	0.37	0.25	-2.01 to 2.51	0.83
	Low	4.70	1.74 to 7.66	**0.002**	3.48	0.52 to 6.45	**0.022**	2.39	-0.13 to 4.91	0.06
TAPSE/PASP ratio continuous (per 0.1 mm/mmHg)		-1.47	-2.13 to -0.82	**<0.001**	-1.30	-1.96 to -0.64	**<0.001**	-1.00	-1.58 to -0.41	**0.001**
TAPSE/PASP ratio tertiles	**High**		(reference)			(reference)			(reference)	
	Intermediate	2.03	-0.73 to 4.79	0.15	2.20	-0.35 to 4.75	0.09	1.00	-1.12 to 3.14	0.35
	Low	6.22	3.44 to 9.00	**<0.001**	5.69	2.99 to 8.39	**<0.001**	4.19	1.82 to 6.57	**<0.001**
B-lines at discharge, per 1		**Model 1**			**Model 2**			**Model 3**		
		beta	**95% CI**	**p-value**	**beta**	**95% CI**	**p-value**	**beta**	**95% CI**	**p-value**
TAPSE continuous (per 1mm)		-0.62	-0.91 to -0.32	**<0.001**	-0.56	-0.85 to -0.26	**<0.001**	-0.31	-0.56 to -0.06	**0.02**
TAPSE tertiles	**High**		(reference)			(reference)			(reference)	
	Intermediate	1.95	-0.62 to 4.52	0.14	1.79	-0.75 to 4.32	0.17	0.70	-1.42 to 2.82	0.52
	Low	4.51	1.96 to 7.07	**<0.001**	3.95	1.40 to 6.50	**0.003**	1.78	-0.38 to 3.94	0.11
TAPSE/PASP ratio continuous (per 0.1 mm/mmHg)		-1.26	-1.80 to -0.73	**<0.001**	-1.16	-1.72 to -0.61	**<0.001**	-0.45	-0.94 to 0.04	0.07
TAPSE/PASP ratio tertiles	**High**		(reference)			(reference)			(reference)	
	Intermediate	1.98	-0.46 to 4.42	0.11	1.76	-0.70 to 4.21	0.16	0.84	-1.25 to 2.92	0.43
	Low	6.67	4.29 to 9.05	**<0.001**	6.35	3.97 to 8.74	**<0.001**	3.72	1.63 to 5.82	**<0.001**

Table 3. Associations of Right Ventricular Function with B-lines Change from Admission to Discharge in Siena Cohort Study

		B-lines change (absolute)						B-lines change (relative)					
		Model 1			Model 2			Model 1			Model 2		
		beta	**95% CI**	**p-value**	**beta**	**95% CI**	**p-value**	**beta**	**95% CI**	**p-value**	**beta**	**95% CI**	**p-value**
TAPSE continuous (per 1mm)		0.42	0.10 to 0.73	**0.01**	0.37	0.06 to 0.69	**0.02**	1.33	0.34 to 2.32	**0.009**	1.12	0.13 to 2.12	**0.03**
TAPSE tertiles	**High**		(reference)			(reference)			(reference)			(reference)	
	Intermediate	-0.66	-0.34 to 2.12	0.64	-0.85	-3.62 to 1.93	0.55	-1.71	-10.61 to 7.19	0.70	-2.31	-11.21 to 6.60	0.61
	Low	-2.59	-5.27 to 0.09	0.06	-2.54	-5.20 to 0.12	0.06	-7.83	-16.25 to 0.59	0.07	-6.98	-15.35 to 1.40	0.10
TAPSE/PASP continuous (per 0.1 mm/mmHg)		0.74	0.07 to 1.41	**0.03**	0.70	0.04 to 1.37	**0.04**	2.34	0.35 to 4.34	**0.02**	2.07	0.03 to 4.11	**0.047**
TAPSE/PASP ratio tertiles	**High**		(reference)			(reference)			(reference)			(reference)	
	Intermediate	-0.95	-3.48 to 1.58	0.46	-0.85	-3.34 to 1.64	0.50	-4.13	-12.20 to 3.93	0.31	-3.70	-11.69 to 4.29	0.36
	Low	-3.80	-6.50 to -1.09	**0.006**	-3.84	-6.52 to -1.16	**0.005**	-11.68	-19.52 to -3.84	**0.004**	-10.77	-18.73 to -2.80	**0.008**

Supplementary table 1. Patient Characteristics

	Nancy (N=36)	Pisa (N=121)	Perugia (N=59)	Siena (N=162)	
ADHF timing	**Admission**	**Admission**	**Discharge**	**Admission**	**Discharge**
Age, yrs	72.4 ± 10.8	71.3 ± 10.6	72.1 ± 10.4	80.0 ± 7.5	80.0 ± 7.5
Women, N (%)	23 (63.9 %)	37 (30.6 %)	18 (30.5 %)	85 (52.5 %)	85 (52.5 %)
Body mass index, kg/m²	-	26.7 ± 4.4	-	27.7 ± 3.4	27.7 ± 3.4
Medical history, N (%)					
Hypertension	-	-	-	111 (68.5 %)	111 (68.5 %)
Diabetes	-	-	-	74 (45.7 %)	74 (45.7 %)
Ischemic heart disease	22 (61.1 %)	50 (41.3 %)	19 (32.2 %)	61 (37.7 %)	61 (37.7 %)
Atrial fibrillation	24 (72.7 %)	35 (28.9 %)	27 (45.8 %)	0 (0 %)	0 (0 %)
Prior HF admission	24 (72.7 %)	113 (94.2 %)	44 (74.6 %)	-	-
Clinical profiles					
NYHA III/IV, N (%)	33 (91.7 %)	72 (59.5 %)	9 (15.3 %)	-	-
Systolic BP, mmHg	118.4 ± 23.7	127.8 ± 24.8	111.9 ± 16.1	128.7 ± 16.3	-
Heart rate, bpm	98.1 ± 15.5	78.8 ± 20.4	76.4 ± 13.3	91.0 ± 7.0	-
Leg edema, N (%)	19 (52.8 %)	40 (33.3 %)	11 (18.6 %)	102 (63.0 %)	27 (16.7 %)
Rales, N (%)	32 (88.9 %)	50 (41.7 %)	18 (30.5 %)	144 (88.9 %)	37 (22.8 %)
Medications, N (%)					
ACEi or ARB	29 (80.6 %)	96 (79.3 %)	37 (62.7 %)	139 (85.8 %)	139 (85.8 %)
Beta-blocker	17 (47.2 %)	32 (26.4 %)	35 (59.3 %)	88 (54.3 %)	88 (54.3 %)
MRA	1 (2.8 %)	79 (65.3 %)	36 (61.0 %)	-	-
Diuretics	36 (100 %)	110 (90.9 %)	59 (100 %)	150 (92.6 %)	150 (92.6 %)
Laboratory findings					
Hemoglobin, g/dl	12.5 ± 2.0	12.4 ± 2.1	12.1 ± 2.4	12.4 ± 2.0	12.4 ± 1.9
Sodium, mmol/l	137.8 ± 3.8	141.3 ± 34.7	140.8 ± 3.8	137.7 ± 4.4	137.4 ± 4.2
eGFR, ml/min/1.73m²	63.6 ± 31.6	58.0 ± 19.8	63.2 ± 22.9	54.2 ± 28.0	47.2 ± 19.9
BNP, pg/ml	804 (589 - 1826)	552 (302 - 1208)	616 (223 - 1152)	1007 (768 - 1530)	582 (335 - 964)
Echocardiography					
LVEF, %	34.9 ± 14.0	36.7 ± 15.5	40.3 ± 16.5	42.0 ± 12.0	42.0 ± 12.0
E/A ratio	1.2 ± 0.3	1.7 ± 1.0	1.9 ± 1.3	1.4 ± 0.7	1.4 ± 0.7
E/e' ratio mean	13.4 ± 4.4	19.2 ± 8.7	18.9 ± 9.6	15.1 ± 3.6	15.1 ± 3.6
TAPSE, mm	14.7 ± 4.7	16.9 ± 4.9	17.3 ± 3.8	19.1 ± 3.3	19.1 ± 3.3
PASP, mmHg	51.5 ± 15.3	50.1 ± 13.6	42.3 ± 13.7	46.6 ± 11.6	46.6 ± 11.6
IVC, mm	22.6 ± 4.9	18.9 ± 4.9	19.8 ± 5.1	22.4 ± 2.6	22.4 ± 2.6
Lung echo					
B-line counts (8 method)	13.5 (8.5 – 18.0)	15.0 (8.0 – 26.0)	4.0 (2.0 – 10.0)	31.0 (27.0 – 36.0)	20.0 (14.0 – 26.0)
B-line counts (28 method)	49.0 (38.0 – 61.5)	21.0 (11.0 – 44.0)	8.0 (5.0 – 34.0)	-	-

Values are mean ± SD, n (%) or median (25th to 75th percentile)

ADHF, acutely decompensated heart failure; HF, heart failure; NYHA, New York Heart Association; BP, blood pressure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; BNP, b-type natriuretic peptide; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure; IVC, inferior vena cava.

Supplementary table 2. Baseline Characteristics according to the Tertiles of TAPSE/PASP ratio

	TAPSE/PASP ratio							
	Admission cohort (N=274)				Discharge cohort (N=221)			
	Low <0.32 (N=100)	Intermediate 0.32-0.44 (N=86)	High >0.44 (N=88)	Adjusted p-value	Low <0.36 (N=77)	Intermediate 0.36-0.50 (N=70)	High >0.50 (N=74)	Adjusted p-value
Age, yrs	75.4 (73.6-77.2)	75.6 (73.4-77.8)	75.2 (73.0-77.4)	0.96	76.7 (74.7-78.6)	76.2 (74.1-78.3)	75.2 (73.2-77.2)	0.56
Women, N (%)	43 (43.0 %)	41 (47.7 %)	43 (48.9 %)	0.82	34 (44.2 %)	31 (44.3 %)	38 (51.4 %)	0.57
Ischemic heart disease	51 (51.0 %)	37 (43.0 %)	28 (31.8 %)	0.08	29 (37.7 %)	22 (31.4 %)	29 (39.2 %)	0.55
Atrial fibrillation	30 (30.3 %)	11 (12.9 %)	6 (6.8 %)	0.28	11 (14.3 %)	8 (11.4 %)	8 (10.8 %)	0.74
Clinical profiles								
Systolic BP, mmHg	118.7 (113.8-123.7)	119.6 (114.1-125.2)	124.1 (118.2-130.0)	0.17	119.0 (115.2-122.8)	120.2 (116.1-124.2)	121.8 (117.9-125.7)	0.56
Heart rate, bpm	91.3 (87.7-95.0)	88.7 (84.6-92.7)	86.9 (82.6-91.2)	0.13	84.7 (82.6-86.8)	83.4 (81.1-85.7)	83.0 (80.8-85.2)	0.47
Leg edema, N (%)	63 (63.0 %)	43 (50.0 %)	49 (55.7 %)	0.13	32 (41.6 %)	29 (41.4 %)	25 (33.8 %)	**0.02**
Rales, N (%)	72 (72.0 %)	66 (76.7 %)	66 (75.0 %)	0.45	42 (54.5 %)	28 (40.0 %)	26 (35.1 %)	**0.002**
ACEi or ARB	89 (89.0 %)	68 (79.1 %)	74 (84.1 %)	0.16	63 (81.8 %)	52 (74.3 %)	61 (82.4 %)	0.23
Beta-blocker	45 (45.0 %)	36 (41.9 %)	41 (46.6 %)	0.55	41 (53.2 %)	38 (54.3 %)	44 (59.5 %)	0.71
Loop	91 (91.0 %)	68 (79.1 %)	74 (84.1 %)	0.30	66 (85.7 %)	55 (78.6 %)	65 (87.8 %)	0.28
Laboratory findings								
Hemoglobin, g/dl	12.3 (11.8-12.7)	12.5 (11.9-13.0)	11.9 (11.3-12.5)	0.21	12.3 (11.8-12.8)	12.1 (11.6-12.6)	12.3 (11.8-12.8)	0.75
Sodium, mmol/l	137.1 (136.0-138.3)	137.2 (135. -138.6)	136.9 (135.6-138.3)	0.94	139.0 (138.0-139.9)	138.6 (137.6-139.6)	139.7 (138.7-140.6)	0.28
eGFR, ml/min/1.73m²	56.4 (51.1-61.7)	58.0 (51.7-64.3)	61.2 (54.8-67.7)	0.46	52.2 (47.4-56.9)	53.3 (48.2-58.5)	60.1 (55.2-65.1)	**0.04**
BNP, pg/ml	1524 (1311-1737)	1090 (829-1351)	997 (736-1259)	**<0.001**	1097 (914-1279)	763 (565-960)	668 (480-857)	**0.002**
Echo parameters								
LVEF, %	35.6 (32.8-38.4)	39.2 (35.8-42.6)	41.0 (37.6-44.4)	**0.03**	40.6 (37.5-43.7)	40.3 (36.9-43.6)	42.5 (39.3-45.7)	0.56
E/A ratio	1.82 (1.59-2.04)	1.38 (1.12-1.63)	1.31 (1.07-1.54)	**<0.001**	2.03 (1.81-2.25)	1.62 (1.39-1.86)	1.40 (1.18-1.61)	**<0.001**
E/e' ratio mean	15.9 (4.9-17.0)	16.1 (14.8-17.4)	15.4 (14.0-16.8)	0.68	18.4 (17.1-19.7)	17.0 (15.5-18.4)	15.5 (14.1-16.9)	**0.009**
TAPSE, mm	13.6 (13.0-14.3)	17.5 (16.8-18.2)	20.7 (19.9-21.5)	**<0.001**	15.7 (15.1-16.3)	18.1 (17.4-18.7)	21.2 (20.5-21.8)	**<0.001**
PASP, mmHg	57.6 (55.7-59.5)	47.3 (45.0-49.6)	35.8 (33.5-38.2)	**<0.001**	55.5 (53.6-57.3)	43.7 (41.8-45.7)	33.0 (31.1-34.9)	**<0.001**
IVC, mm	23.2 (22.5-24.0)	21.2 (20.3-22.0)	19.6 (18.7-20.5)	**<0.001**	22.9 (22.2-23.7)	20.7 (19.9-21.5)	19.5 (18.8-20.3)	**<0.001**
TAPSE/PASP, mm/mmHg	0.24 (0.23-0.26)	0.38 (0.35-0.40)	0.60 (0.58-0.62)	**<0.001**	0.29 (0.27-0.32)	0.42 (0.39-0.45)	0.66 (0.64-0.69)	**<0.001**
B-lines	24.4 (22.4-26.3)	20.2 (17.9-22.5)	18.1 (15.8-20.5)	**<0.001**	17.2 (15.5-18.9)	12.5 (10.7-14.4)	10.6 (8.8-12.3)	**<0.001**

Values are adjusted mean (95% confidence interval) and n (%). Linear regression or logistic regression was used to adjust for study difference.

TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure; BP, blood pressure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; BNP, b-type natriuretic peptide; LVEF, left ventricular ejection fraction; IVC, inferior vena cava.

Supplementary table 3. Association of TAPSE and TAPSE/PASP Ratio with B-line Counts across LVEF Strata

	Admission					Discharge			
	TAPSE tertiles					TAPSE tertiles			
	T1	**T2**	**T3**	**adjusted P**		**T1**	**T2**	**T3**	**adjusted P**
Reduced EF (N=151)	25.1 (22.0 - 28.3)	20.9 (17.5 - 24.3)	19.6 (16.1 - 23.2)	0.06	**Reduced EF (N=92)**	17.2 (14.8 - 19.6)	14.0 (11.4 - 16.7)	10.7 (7.3 - 14.1)	**0.01**
Mid-range EF/ preserved EF (N=168)	21.0 (18.4 - 23.5)	20.0 (17.2 - 22.7)	18.2 (15.1 - 21.3)	0.36	**Mid-range EF/ preserved EF (N=129)**	13.7 (11.3 - 16.1)	12.3 (9.6 - 15.0)	11.3 (8.4 - 14.2)	0.37
	TAPSE/PASP tertiles					**TAPSE/PASP tertiles**			
	T1	**T2**	**T3**	**adjusted P**		**T1**	**T2**	**T3**	**adjusted P**
Reduced EF (N=125)	24.1 (21.1 - 27.1)	23.6 (20.3 - 26.9)	19.0 (15.4 - 22.6)	**0.043**	**Reduced EF (N=92)**	17.5 (14.8 - 20.2)	14.2 (11.4 - 17.0)	12.5 (9.8 - 15.2)	**0.03**
Mid-range EF/ preserved EF (N=149)	22.7 (19.9 - 25.5)	19.7 (16.5 - 22.8)	17.2 (14.0 - 20.3)	**0.014**	**Mid-range EF/ preserved EF (N=129)**	17.1 (14.6 - 19.5)	10.9 (8.3 - 13.4)	9.9 (7.6 - 12.3)	**<0.001**

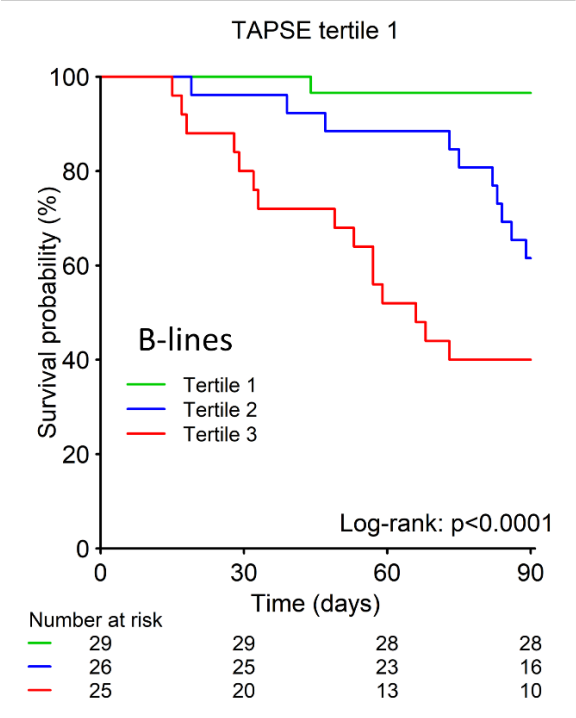
Values are adjusted mean (95% confidence interval). Linear regression was used to adjust for study difference.

Supplementary table 4. Associations of Right Ventricular Function with B-lines at Admission and Discharge after adjustment for E/e' ratio and BNP

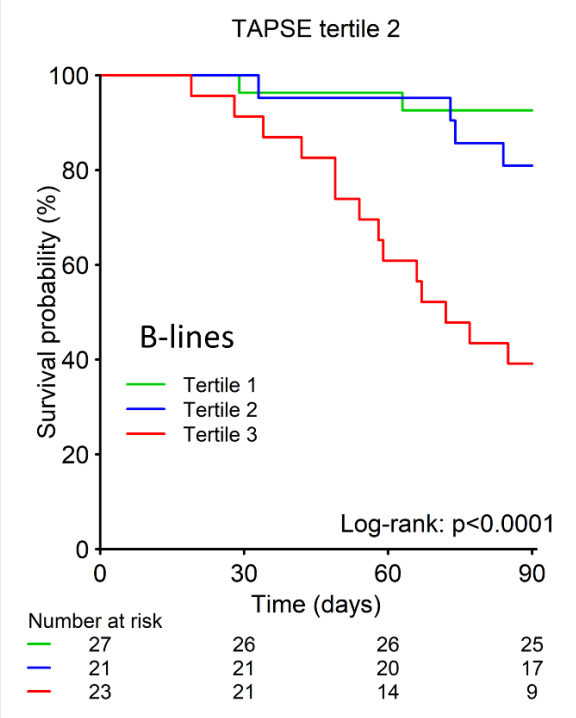
B-lines at admission, per 1		**Model**	
		beta (95%CI)	**p-value**
TAPSE continuous (per 1mm)		-0.08 (-0.35 to 0.19)	0.55
TAPSE tertiles	**High**	(reference)	
	Intermediate	0.56 (-1.78 to 2.90)	0.64
	Low	1.31 (-1.23 to 3.85)	0.31
TAPSE/PASP ratio continuous (per 0.1 mm/mmHg)		-1.12 (-1.68 to -0.56)	**<0.001**
TAPSE/PASP ratio tertiles	**High**	(reference)	
	Intermediate	1.52 (-0.71 to 3.75)	0.18
	Low	4.86 (2.45 to 7.26)	**<0.001**
B-lines at discharge, per 1		**Model**	
		beta (95%CI)	**p-value**
TAPSE continuous (per 1mm)		-0.28 (-0.53 to -0.03)	**0.03**
TAPSE tertiles	**High**	(reference)	
	Intermediate	0.82 (-1.28 to 2.91)	0.44
	Low	1.62 (-0.52 to 3.76)	0.14
TAPSE/PASP ratio continuous (per 0.1 mm/mmHg)		-0.48 (-0.94 to -0.01)	**0.048**
TAPSE/PASP ratio tertiles	**High**	(reference)	
	Intermediate	0.73 (-1.29 to 2.76)	0.48
	Low	3.76 (1.71 to 5.80)	**<0.001**

Model; adjusted for cohort, E/e' ratio and brain natriuretic peptide transformed by natural logarithm.

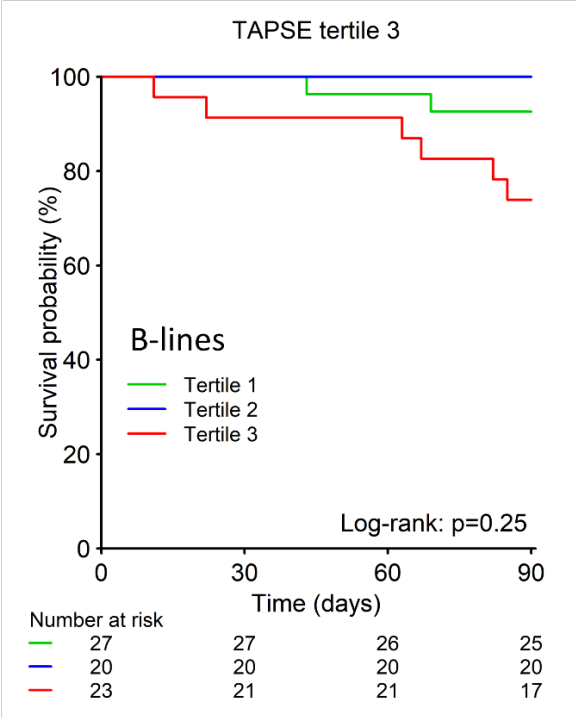
Supplementary figure 1. Kaplan-Meier Survival Curves for the Primary Outcome according to the Cohort Study Specific Tertiles of B-line Counts at Discharge across Subgroups Defined by TAPSE Tertiles



	Absolute risk difference at 90 days
B-lines T3 vs T1	53.1% (31.8 – 74.4)
B-lines T2 vs T1	31.6% (10.7 – 52.4)



	Absolute risk difference at 90 days
B-lines T3 vs T1	53.5% (31.2 – 75.7)
B-lines T2 vs T1	11.6% (-7.8 – 31.1)



	Absolute risk difference at 90 days
B-lines T3 vs T1	18.7% (-1.8 – 39.2)
B-lines T2 vs T1	-7.4% (-17.3 – 2.5)