Liver Stiffness for Predicting Adverse Cardiac Events in Chinese Patients With Heart Failure: A Two-year Prospective Study

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Research

Keywords: Heart failure, liver stiffness; prognosis, tricuspid annual plane systolic excursion, Echocardiography

Posted Date: March 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-295000/v1

Version of Record: A version of this preprint was published at BMC Cardiovascular Disorders on February 14th, 2022. See the published version at https://doi.org/10.1186/s12872-022-02497-w.

Abstract

Background. To investigate whether liver stiffness (LS) can predict adverse cardiac events in Chinese patients with heart failure (HF).

Methods. Total of 53 hospitalized patients with HF were enrolled and LS and tricuspid annual plane systolic excursion (TAPSE)were determined before discharge with Fibroscan® and Echocardiography. The patients were divided into two groups: High LS group(LS >6.9Kpa, n=23) and Low LS group(LS ≤6.9Kp, n=30) . Patients were followed up for 24 months at interval of 3 months. The endpoint of follow-up is death or rehospitalization for HF.

Results. All patients were followed up for 24 months or until the endpoint. Patients in High LS group had lower platelet count(P=0.014), lower creatine clear rate (P=0.014), higher level of B-type natriuretic peptide at discharge(P=0.012), and lower tricuspid annual plane systolic excursion (P<0.001). During 24 months follow-up, 3(5.7%) deaths and 21(39.6%) hospitalization were observed. Patients in high LS group had a higher rate of death/rehospitalization when compared with patient in low LS group (Hazard ratio: 4.81; 95% confidence interval:1.69-13.7, P=0.003) after adjustment for age, sex, platelet count, creatine clear rate, and B-type natriuretic peptide level. Also, TAPSE≤16 can predict adverse cardiac events with HR of 6.63 (95% confidence interval:1.69-13.7, P=0.004) for age, sex, platelet count, creatine clear rate, and B-type natriuretic peptide level.

Conclusion. LS and TAPSE may be considered for predicting worse outcomes for patients with heart failure.

1. Introduction

Patients with heart failure face high rates of mortality and rehospitalization. Multiple studies are trying to identify predictors of worse prognosis in these patients [1-2]. Recent studies show that right ventricle dysfunction plays a key role in hemodynamic and prognosis of patients with heart failure. Right ventricle failure implies an increased risk of cardiac adverse events, regardless of left ventricle dysfunction degree [3-4]. For patients with right ventricle failure, increased right-sided filling pressure may cause abnormal liver function test and liver congestion. However, liver congestion may cause the increase of liver stiffness which can be quantified by liver stiffness measurements [5].

Liver stiffness measurements with transient elastography (FibroScan®) were first developed to evaluate liver fibrosis noninvasively. Further studies show decompensated heart failure may increase liver stiffness value measured by transient elastography [6] and liver stiffness may reflect right-side filling pressure in patients with heart failure [7]. Recent several studies show liver stiffness measured by transient elastography is promising for prognosis prediction in patients with heart failure [8]. However, data about the efficacy of liver stiffness for predicting long-term prognosis of heart failure patients are still limiting. Also, tricuspid annual plane systolic excursion (TAPSE) is reported to be related to the prognosis of patients with HF[9]. But data about long-term follow-up of TAPSE and prognosis of Chinese patients is limiting. In this study, we prospectively enrolled patients with heart failure in a tertiary hospital to evaluate efficacy of liver stiffness and TAPSE for predicting 2 years adverse events.

2. Methods

2.1. patients. Hospitalized patients with heart failure between June 2018 to December 2018 were screened at Beijing Ditan Hospital of Capital Medical University. The diagnosis of heart failure was according to 2018 Chinese guidelines for the diagnosis and treatment of chronic HF. Patients were given individualized therapy and were discharged according to related guideline [10]. Patients were excluded when met these criteria: ▯ previous diagnosis of chronic liver disease; ▯HBsAg positive and/or HCV RNA positive; ▯ultrasound, Abdominal CT and/or MRI showed signs of chronic liver diseases, cirrhosis, portal hypertension and/or liver cancer; ▯ patients who cannot get valid liver stiffness tests. This study was approved by the Institutional ethics committee of Beijing Ditan Hospital (No. 2018-070-12). Written Informed consent was obtained from all patients.

2.2. Follow-up and Endpoints. Total of 53 patients were enrolled and followed up every 3 months by clinical visits or through telephone interviews. The patients were divided into two groups: High LS group(LS >6.9Kpa, n=23) and Low LS group(LS ≤6.9Kp, n=30) according previous study [7]. The primary endpoint was the combination of cardiac death or rehospitalization for the heart failure. For patients who experienced more than 1 cardiovascular events, only the first event was used for analysis.

2.3. Demographic information and laboratory test. Data regarding demographic information, physical examination, laboratory index, echocardiography, co-morbidities medications were documented. All patients got tests of complete blood count, liver function tests, kidney function tests, and serum B-type natriuretic peptide (BNP) when discharged.

2.4. Echocardiography and liver stiffness measurements. Echocardiography was performed with a EPIQ 5 device (Philips, Netherlands) when discharged by an experienced ultrasonography physician. Especially, tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode echocardiography with the cursor optimally aligned along the direction of the tricuspid lateral annulus in the apical four-chamber view. Right ventricular dysfunction(RVD) was defined as TAPSE ≤16 mm according to related guideline[11].LS measurements were performed before discharged with a Fibroscan® device (Echosens, France) according to manufacturer’s instructions. The measurements were expressed in Kpa and corresponded to the median values of 10 acquisitions with a success rate of at least 60% and an IQR less than 10% [12].

2.5. Statistical analysis. SPSS 22.0 was used for data analysis. All data were tested for normal distribution and homogeneity of variance. Continuous variables were expressed as mean values ± standard deviation (mean ± SD) or median (interquartile interval) [M(Q25-Q75)], and categorical variables were expressed as an example (%). T-test was used for the mean comparison of normal distribution measurement data between the two groups, Wilcoxon rank sum test and Mann-Whitney test were used for the comparison of non-normal distribution continuous variables. chi-square test was used for the comparison of categorical variables. Kaplan–Meier curves and log-rank test were used to describe and compare time to events. Cox proportional hazards regression models were used to examine the independent association of liver stiffness/TAPSE and the risk of adverse outcomes, and age, sex and potential covariates were included in the model. All P-values reported were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

3.1 Study population. As previous studies showed heart failure patients with LS >6.9Kpa had higher rate of HF rehospitalization and cardiac death [7], we divided our patient into two groups: High LS group(LS >6.9Kpa, n=23) and Low LS group(LS ≤6.9Kpa, n=30). The demographic characteristics and clinical data of the total population and two groups was showed in table 1. There is no difference in age, sex ratio, ratio of NYHA class III/IV patients between patient in different LS level groups. However, Patients in high LS group showed higher BNP level(P=0.012) and lower Platelet count(P=0.014), Ccr(P=0.014), and TAPSE(P<0.001).

3.2. LS for prediction of adverse event in heart failure patients. All patients were followed up for 24 months or till the endpoint. Total of 24(45.3%) patients experienced adverse events during 24 months follow-up, which include 3 deaths (5.7%). Kaplan-Meier curves showed that patients in high LS group showed higher risk of endpoint events when compared with patients in the low LS group (log-rank test p<0.001) (Figure 1). In univariate Cox regression analysis, risk of adverse cardiac events increases to 7.86 times(95% confidence interval[CI]:3.08 to 20.06; p<0.001) in HF patients with LS>6.9Kpa when compared with patients with LS≤6.9Kpa. Per 1 Kpa increase of LS predict the risk of adverse events with the hazard ratio (HR) of 1.08(1.04-1.14, P=0.001). In multivariable Cox regression analysis, LS> 6.9Kpa can still predict adverse cardiac events with HR of 4.81(1.69-13.7, P=0.003) after adjust for age, sex, Ccr, ln (BNP), and platelet count (table 2).

3.3. Tricuspid annual plane systolic excursion (TAPSE) for prediction of adverse event in heart failure patients. As TAPSE is an key Echocardiography parameter to reflect RV function, Kaplan-Meier curves were also constructed to compare the prognosis of HF patients between patients with TAPSE≤16 mm and patients with TAPSE>16mm(Figure 2) . Patients with TAPSE≤16 mm showed higher risk of cardiac events when compared with patients with TAPSE>16mm(log-rank test p<0.001). In univariate Cox regression analysis, risk of adverse cardiac events increases to 6.82 times(95% CI:2.90 to 16.01; p<0.001) in HF patients with TAPSE≤16 mm when compared with patients with L TAPSE>16mm. In multivariable Cox regression analysis, TAPSE≤16 can still predict adverse cardiac events with HR of 6.63(1.84-23.96, P=0.004) after adjust for age, sex, Ccr, ln (BNP), and platelet count (table 3).

4. Discussion

Recent studies showed liver stiffness is promising in predicting prognosis of patients with heart failure. Yet the cut-off of LS for predicting prognosis is controversial and long-term follow-up data of patients is lacking [13]. In Saito's study [14], 105 acute decompensated heart failure patients were followed up for mean 153 days. HF patients with LS>8.8Kpa had a significantly higher rate of cardiac event. However, in Taniguchi's study [7], 171 HF patients were followed up for mean 203 days, patients with LS>6.9 Kpa had higher risk for cardiac event. In this study, we chose 6.9Kpa as cut-off of LS and showed LS LS>6.9 Kpa can predict higher risk of cardiac events in 24 months follow-up. This study provides more data to support the use of LS in long-term management of patients with HF.

As liver stiffness measurement is not always available for HF patients, TAPSE from echocardiography measurement is another well-established parameter to evaluate RV function. In this study, HF patients with TAPSE≤16 mm had higher risk for cardiac events in 2 years follow-up. This result is in accordance with previous studies [15,16]. TAPSE can also be a important parameter for predicting prognosis of patients with HF.

The rational of LS for predicting prognosis of HF is that LS is correlated to central venous pressure, a comprehensive index to reflect both RV dysfunction and preload increase related to Left ventricular dysfunction [17, 18]. Besides Liver stiffness measured by Fibroscan, there are also studies to use Fibrosis-4, NFS non-alcoholic fatty liver disease fibrosis score (NFS) for predicting prognosis of HF patients [19, 20]. Recently Saito reported spleen stiffness measured by two-dimensional SWE, another method for measuring organ stiffness can predicting prognosis of patients with heart failure [21]. Abdominal viscera stiffness is promising for predicting prognosis of HF patients.

However, this is a single-centered study and sample size is limiting. Further multi-centered studies with large sample size are needed to verify the results Chinese HF patients. Also, dynamics of liver stiffness during follow-up can be monitored to show its correlation with patients' prognosis.

5. Conclusion

In conclusion, this study showed that LS when discharged and TAPSE can be used for predicting 2 years prognosis of patients with HF. Patients with LS > 6.9 Kpa and/or TAPSE ≤ 16 mm should be monitored more closely for possible adverse cardiac events

Declarations

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest in this work.

Acknowledgements

This study was funded by National Science and Technology Major Project (2017ZX10202202, 2018ZX10715-005); High-level innovative expert project of Qinghai province (2019-24), Tianqing Foundation of Chinese Foundation for hepatitis prevention and control (TQGB20210050), and Yumiao Project of Beijing Ditan Hospital of Capital Medical University (DTYM201813).

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Tables

Table 1. Clinical Characteristics of the study population

	Overall(n=53)	LS≤6.9kPa(n=30)	LS>6.9kPa(n=23)	P value
Clinical Characteristics				
Age, yrs	65.5±12.8	64.36±13.56	67.04±11.94	P=0.457
Male,n%	39(73.6)	22(73.3)	17(73.9)	P=0.962
NYHA class III/IV, n%	44(83.0)	23(76.7)	21(91.3)	P=0.300
Systolic BP, mmHg	122.79±17.47	125.63±17.38	119.09±17.25	P=0.178
Diastolic BP, mmHg	71.49±10.13	73.33±10.42	69.09±9.42	P=0.132
Comorbidities				
CAD, n%	35(66.0)	17(56.7)	18(78.3)	P=0.100
AF, n%	8(15.1)	4(13.3)	4(17.4)	P=0.983
Hypertension, n%	39(73.6)	22(73.3)	17(73.9)	P=0.962
Diabetes,n%	23(43.4)	11(36.7)	12(52.2)	P=0.259
Laboratory parameters				
Hemoglobin, g/l	126.5±20.9	128.9±20.2	123.5±21.9	P=0.358
Platelet count,10^9/L	192(161.5-249)	212.5(177.5-266.5)	175(139-230)	P=0.014
Ccr, %	73.14±25.78	79.97±23.30	62.46±25.83	P=0.014
BNP, pg/ml	344(146-828)	174.5(111-568)	500(187.5-1535)	P=0.012
AST, U/L	19.9(15.8-29.4)	19.3(15.8- 23.6)	20.0(14.85-30.25)	P=0.560
ALT, U/L	19.6(13.15-28.5)	18.7(13.15- 27.1)	20.7(13.1-30.45)	P=0.872
Echocardiographic parameters				
LVEDD, mm	58.0(51.5-62.0)	57.5(52.0- 61.5)	59.0(48.5-62.0)	P=0.844
LVEF, n%	40.32±11.20	39.95±9.97	40.81±12.8	P=0.785
LADD,mm	44.11±7.26	43.47±5.72	44.96±8.96	P=0.465
Moderate/Severe MR, n%	25(47.2)	12(40)	13(56.5)	P=0.232
Moderate/Severe TR,n%	17(32.1)	8(26.7)	9(39.1)	P=0.335
TAPSE≤16mm, n%	18(34.0)	4(13.3)	14(60.9)	P=0.0003

AF: atrial fibrillation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BNP: B-type natriuretic peptide; BP: blood pressure; CAD: coronary artery disease; Ccr: creatinine clearance; LS: liver stiffness; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; TAPSE: tricuspid annual plane systolic excursion; TR: tricuspid regurgitation.

Table 2. Association between LS and risk of cardiac event of patients with HF

	Univariate		Multivariable	
	HR	P value	HR	P value
LS>6.9kPa	7.86(3.08-20.06)	<0.001	4.81(1.69-13.7)	0.003
LS (per 1kPa increase)	1.08(1.04-1.14)	0.001		
Ccr (per 1ml/min increase)	0.98(0.97-1.00)	0.016	0.99(0.98-1.00)	0.308
PLT (per 1×10^9/L increase)	0.99(0.99-1.00)	0.036	1.00(0.99-1.00)	0.337
LnBNP (per 1 increase)	1.68(1.22-2.30)	0.001	1.38(0.98-1.96)	0.069
TAPSE≤16mm	6.82(2.90-16.01)	<0.001		

HF: heart failure; LS: liver stiffness; Ccr: creatinine clearance rate; PLT: platelet; LnBNP: natural logarithms of B-type natriuretic peptide.

Multivariable Cox analysis model 1= adjusted by age, sex, Ccr, ln(BNP),and platelet.

Table 3. Association between TAPSE and risk of cardiac event of patients with HF

	Univariate		Multivariable	
	HR	P value	HR	P value
Ccr (per 1ml/min increase)	0.98(0.97-1.00)	0.004	0.99(0.93-1.02)	0.976
PLT (per 1×10^9/L increase)	0.99(0.99-1.00)	0.036	1.00(0.99-1.00)	0.996
LnBNP (per 1 increase)	1.68(1.22-2.30)	0.001	1.38(0.93-1.02)	0.928
TAPSE≤16mm	6.82(2.90-16.01)	<0.001	6.63(1.84-23.96)	0.004

TAPSE: tricuspid annual plane systolic excursion; HF: heart failure; LS: liver stiffness; Ccr: creatinine clearance rate; PLT: platelet; LnBNP: natural logarithms of B-type natriuretic peptide.

Multivariable Cox analysis model = adjusted by age, sex, Ccr, ln(BNP),and platelet.

Figures

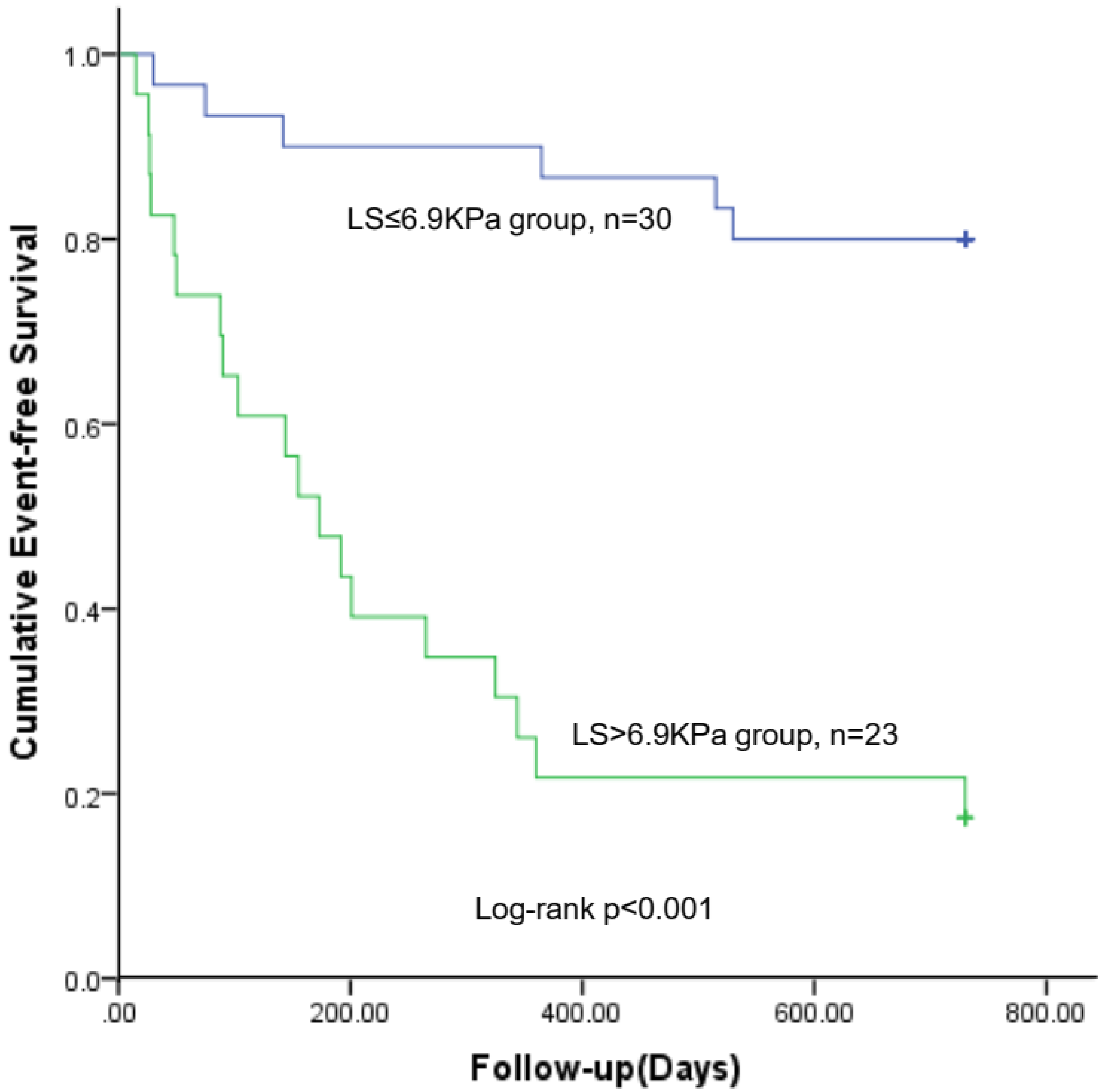

Figure 1

Kaplan-Meier analysis between patients in High LS group(LS>6.9Kpa,n=23) and Low LS group(LS≤6.9 Kpa,n=30). LS: liver stiffness.

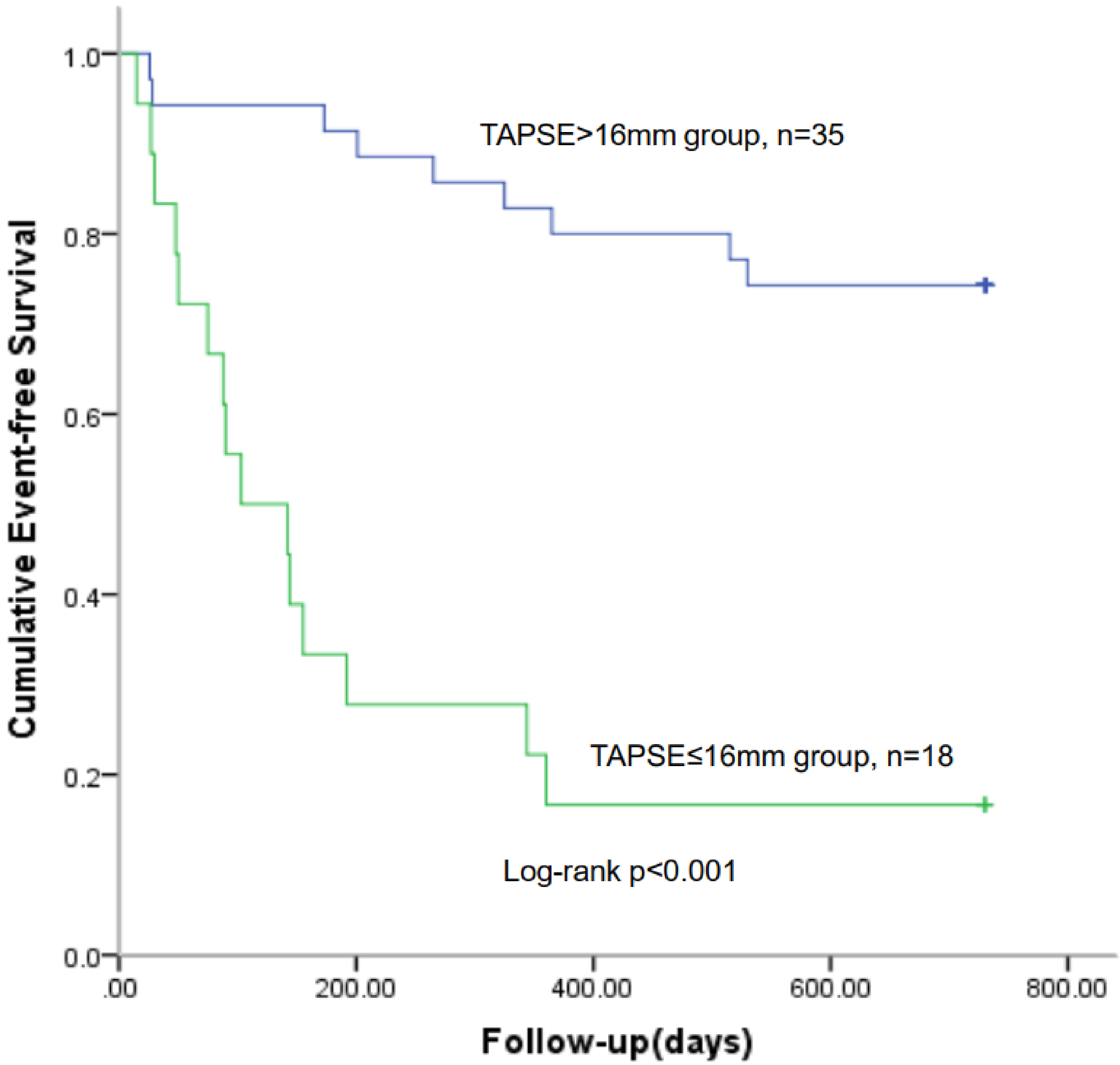

Figure 2

Kaplan-Meier analysis between patients with TAPSE>16mm,n=35 and patients with TAPSE≤16mm,n=18. TAPSE: tricuspid annual plane systolic excursion.