Prognostic value of the severity of tricuspid regurgitation on Doppler echocardiography in patient with heart failure with reduced ejection fraction

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ABSTRACT

Background: Tricuspid regurgitation severity has recently gained attention as a prognostic predictor of outcome events in patients who have left-sided heart failure. This study sought to define the relationship between tricuspid regurgitation and outcome in patients with heart failure with reduced ejection fraction.

Objective: To investigate the characteristics of tricuspid regurgitation by Doppler echocardiography in patients with heart failure and reduced ejection fraction. To explore the association between the severity of tricuspid regurgitation and short-term mortality and hospital readmission in the study patients.

Methods: 116 heart failure-reduced ejection fraction patients were enrolled in this study, followed up, and evaluated after 3 - 6 months.

Results: 48.3% of patients have mild tricuspid regurgitation, 33.6% of patients have moderate tricuspid regurgitation, and 18.1% of patients have severe tricuspid regurgitation. 47 events (40.5%) occurred: 11 deaths (9.5%) and 38 readmissions (32.8%). A Kaplan - Meier curve showed that the survival rate of the severe tricuspid regurgitation group was significantly lower than the group with mild to moderate tricuspid regurgitation. A multivariate Cox regression model identified that tricuspid regurgitation severity was an independent predictor of 3-to-6-month mortality or readmission (HR 1.94; CI 95% 1.30 - 2.91).

Conclusion: Tricuspid regurgitation severity was an independent predictor of reduced ejection fraction in patients with heart failure.

Keywords: tricuspid regurgitation, mortality.

INTRODUCTION

Heart failure is a clinical syndrome caused by structural and/or functional changes in the heart due to various pathological causes. The disease has a high incidence, mortality rate, and treatment costs[1]. According to updated 2021 statistics from the American Heart Association, it is estimated that the prevalence of heart failure is around 6 million people, accounting for 1.8% of the total US population[2] and over 23 million people worldwide. It is estimated that by 2030, there will be over 8 million people (1 in 33 people will have heart failure). Therefore, heart failure remains a top concern in public health care.

In recent years, much data has

shown that significant (moderate-severe) tricuspid regurgitation can lead to impaired function and reduced survival, especially in patients with heart failure. There have been increasing studies on the characteristics and prognostic value of tricuspid regurgitation, from which appropriate and timely treatment options are proposed, reducing the burden of disease caused by tricuspid regurgitation.

Echocardiography is currently the most widely used method to assess the degree of tricuspid regurgitation. In Vietnam, there have been very few studies examining in detail the prognostic value of tricuspid regurgitation in patients with heart failure and EF < 40%. Therefore, we conduct the research topic **"Prognostic value of tricuspid regurgitation severity on echocardiography in patients with heart failure and reduced ejection fraction"** with two objectives:

Clinical and subclinical characteristics in hospitalized patients with heart failure and reduced ejection fraction.

The value of tricuspid regurgitation severity on echocardiography in predicting mortality and heart failure rehospitalization in the above group of patients.

OBJECTS AND METHODS

* Patient selection criteria

All study patients have been diagnosed with heart failure with reduced EF according to 2021 ESC guidelines. Patients agreed to participate in the study.

* Exclusion criteria

Patients with organic tricuspid valve disease, severe left-sided valve disease, other valve diseases due to rheumatic heart disease, prosthetic valves, congenital heart disease, and pacemaker implantation. Patients with COPD, asthma, other chronic or acute lung diseases, end-stage renal disease on dialysis, patients with poor echocardiographic images, patients with acute internal or surgical conditions, and patients who refused to participate in the study.

* Study setting

Study patients were recruited at the Vietnam National Heart Institute.

* Research methods

Study design

Retrospective study: patients were hospitalized from August 2020 to July 2021, all patients were followed up until August 2022.

Prospective study: patients hospitalized from September 2022 to June 2023, all patients will be followed up until September 2023.

Sampling method and sample size

Convenience sampling: Hospitalized patients.

Data collection

- All admitted patients underwent medical history, physical examination for signs and symptoms of heart failure, and necessary investigations (ECG, chest X-ray, NT-proBNP, echocardiography) to meet the diagnostic criteria for heart failure with reduced EF and did not have exclusion criteria.

- Perform echocardiography according to the research protocol to collect tricuspid regurgitation parameters as required.

- Follow up with patients during hospitalization and after discharge to assess outcomes: all-cause mortality, heart failure rehospitalization based on the interview questionnaire.

- Echocardiographic parameters were measured according to the American Society of Echocardiography guidelines. The severity of tricuspid regurgitation was classified based on 3 parameters: Vena Contracta width (VC), regurgitant jet area, and the ratio of tricuspid regurgitant area to right atrial area. VC was used as the diagnostic criterion for grading tricuspid regurgitation, and the other two parameters were additionally evaluated for comparison. Vena Contracta is the narrowest part of the regurgitant jet as it passes through the tricuspid valve, measured on the four-chamber view from the color Doppler aliasing, defining tricuspid regurgitation severity based on Vena Contracta: mild <0.3cm, moderate: 0.3-0.69cm, and severe ≥0.7cm.

Data analysis

All collected data will be analyzed using standard statistical methods on a computer with SPSS software version 20.0.

RESULTS

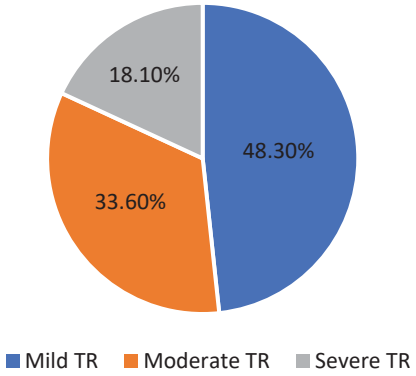

***Figure 1**. Distribution of tricuspid regurgitation severity in the study population*

Among 116 study patients, mild tricuspid regurgitation was the most common at 48.3%. This was followed by moderate (33.6%) and severe tricuspid regurgitation (18.1%).

General characteristics of study subjects

***Table 1**. Clinical and subclinical characteristics in the study patients*

Characteristics	Overall (n =116)	Mild TR (n=56)	Moderate TR (n=39)	Severe TR (n= 21)	p
Age	63.0±14.2	61.7±14.1	65.6±14.5	61.4±13.7	0.363
Male	86 (74.1)	39 (69.6)	30 (76.9)	17 (81.0)	0.534
Heart rate	94.3±22.4	87.5±20.7	100.2±20.5	101.7±25.7	**0.005**
Troponin T	40 (24 – 84.8)	31 (20.3 - 241)	30.4 (24.4 -75.3)	56.5 (33- 94.5)	0.317
NYHA I	11 (9.5)	6 (10.7)	4 (10.3)	1 (4.7)	0.587
NYHA II	43 (37.1)	23 (41.1)	13 (33.3)	7 (33.3)	0.587
NYHA III	55 (47.4)	26 (46.4)	18 (46.2)	11 (52.4)	0.587
NYHA IV	7 (6.0)	1 (1.8)	4 (10.3)	2 (9.5)	0.587
NT-proBNP	1575 (444 - 4657)	807 (300 - 2841)	1503 (444 - 4687)	4829.5 (2467 - 7134)	**0.007**
Creatinine	117.7±79.5	104.4±91.3	124.7±64.3	139.8±66.6	**0.0014**
SBP	121.4±21.1	123.0±20.2	120.7±21.3	118.7±23.7	0.713

Our study was conducted on a total of 116 patients hospitalized with heart failure and EF <40%, of which 74.1% were male, with a mean age of 63.0±14.2. Among the 116 study patients, 3 patients died in the hospital, the total deaths during follow-up were 11 patients (9.5%), and 38 patients (32.8%) were rehospitalized for heart failure. Total events were 47 patients, accounting for 40.5%. Heart rate, NT-proBNP level, creatinine in the severe tricuspid regurgitation group were statistically significantly higher than the mild and moderate groups (p<0.01).

***Table 2**. Echocardiographic characteristics in the study of patients*

Parameters	Overall (n =116)	Mild TR (n=56)	Moderate TR (n=39)	Severe TR (n= 21)	p
LA size	42.1±7.2	40.2±5.1	42.1±7.8	47.2±8.5	**0.0005**

Parameters	Overall (n =116)	Mild TR (n=56)	Moderate TR (n=39)	Severe TR (n= 21)	p
LVEDD	60.3±8.8	60.3±8.1	59.0±8.2	62.8±8.8	0.241
LVESD	50.8±9.1	50.5±9.3	49.5±8.8	53.9±9.0	0.200
EF biplane	29.9±6.3	30.9±6.8	29.4±5.8	28.4±5.7	0.186
RVID1	37.3±9.2	34.8±4.6	37.9±6.9	42.9±9.2	**< 0.0001**
RVID2	29.5±6.2	27.6±4.5	29.9±5.7	34.0±8.8	**0.0002**
RVID3	*71.4±9.3*	*70.7±8.3*	*70.7±9.7*	*74.7±11.1*	0.211
TAPSE	17.5±3.6	18.6±3.4	16.8±3.9	16.0±3.1	**0.005**
FAC	35.4±8.6	37.9±7.6	34.8±8.4	29.5±9.0	**0.0004**
RVSP	41.1±15.0	32.8±8.6	44.4±14.3	57.1±14.8	**0.0001**
TR jet area	5.0±4.6	1.8±1.8	5.7±3.0	12.1±3.7	**0.0001**
Vena Contracta	3.8±3.5	1.3±0.7	4.4±1.2	9.8±3.2	**0.0001**
RA area	18.6±7.1	14.6±3.5	19.6±5.5	27.6±8.1	**0.0001**
TR jet/RA ratio	0.23±0.17	0.11±0.08	0.28±0.13	0.45±0.11	**0.0001**
TR jet direction					
Eccentric	27 (23.3)	0 (0.0)	7 (18.0)	20 (95.2)	**< 0.001**
Central	89 (76.7)	56 (100)	32 (82.1)	1 (4.8)	
Mitral regurgitation					
Mild	33 (29.2)	25 (45.5)	7 (18.9)	1 (4.8)	**< 0.001**
Moderate	35 (31.0)	19 (34.5)	12 (32.4)	4 (19.1)	
Severe	45 (39.8)	11 (20.0)	18 (48.7)	17 (76.2)	
Aortic regurgitation					
Mild	60 (83.3)	29 (93.6)	20 (80.0)	11 (68.8)	0.042
Moderate	9 (12.5)	1 (3.2)	3 (12.0)	5 (31.5)	
Severe	3 (4.2)	1 (3.2)	2 (8.0)	0 (0.0)	

The mean LVEF (biplane) was 29.9 ± 6.3%, with no difference between the study groups. The mean left atrial diameter was 47.2 ± 8.5mm. The left atrial size in the severe TR group was larger than the mild and moderate TR groups; this difference was statistically significant (p<0.01). The right ventricle in the severe TR group was more dilated compared to the mild-moderate TR groups with larger transverse and longitudinal diameters (p<0.01). The RVSP and right ventricular systolic function parameters like TAPSE and FAC were also higher in the severe TR group compared to the other two groups (p<0.01). Regarding echocardiographic parameters of tricuspid regurgitation, TR jet area, vena Contracta width, and the ratio of TR jet area to the right atrial area were larger in the severe TR group compared to the other two groups (p<0.01). Most severe TR jets were eccentric, while central jets were commonly seen in mild-moderate TR. There was a correlation between mitral regurgitation and tricuspid regurgitation severity, with severe mitral regurgitation having a higher rate of severe tricuspid regurgitation compared to the other two groups (p<0.01). There was no correlation between tricuspid regurgitation severity and aortic regurgitation severity.

Prognostic value of tricuspid regurgitation severity on echocardiography in predicting short-term mortality and rehospitalization in the study patients.

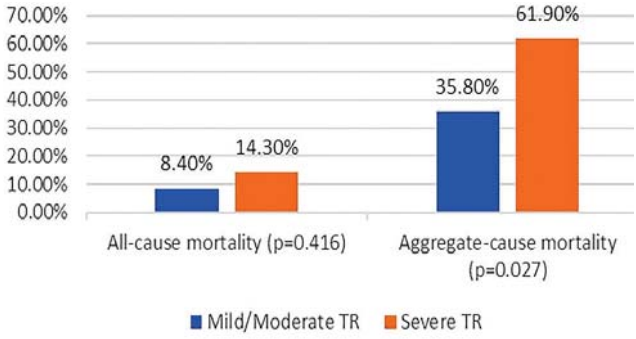

***Figure 2**. Rates of combined events and mortality according to tricuspid regurgitation severity*

- At the end of the study, the rate of combined events in the severe tricuspid regurgitation group was statistically significantly higher compared to the mild and moderate tricuspid regurgitation groups (61.9% vs 35.8% p = 0.027).

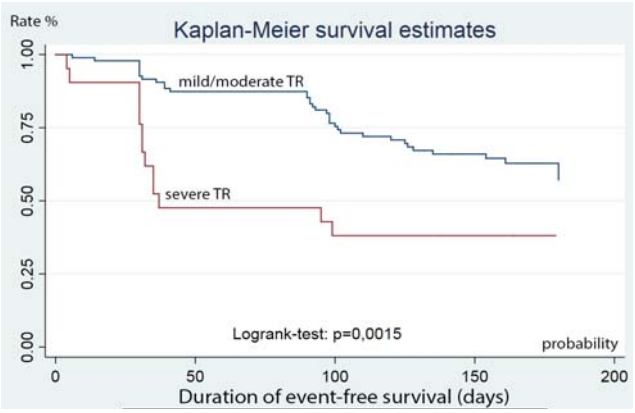

***Figure 3**. Kaplan-Meier curves showing event-free survival probability according to tricuspid regurgitation severity*

Comparison of event-free survival rates according to tricuspid regurgitation severity at 3-6 months of follow-up showed statistically significant differences p=0.0015.

***Table 3**. Univariate and multivariate regression models of tricuspid regurgitation severity and other prognostic factors with combined events*

	Univariate		Multivariate	
	HR(95%CI)	P	HR(95%CI)	P
Age	1.01 (0.98 - 1.02)	0.592		
Male	0.88 (0.47 - 1.63)	0.676		
Smoking	0.68 (0.34 - 1.37)	0.281		
Hypertension	0.74 (0.42 - 1.32)	0.315		
Atrial fibrillation	1.20 (0.61 - 2.36)	0.603		
Heart failure history	0.54 (0.07 - 3.90)	0.539		
Admission SBP	0.99 (0.98 - 1.01)	0.496		
Heart rate	1.01 (0.99 - 1.02)	0.612		
NYHA	1.23 (0.83 - 1.82)	0.302		
Hemoglobin	0.99 (0.97 - 1.002)	0.098	0.98 (0.96 - 0.99)	**0.002**
Serum creatinine	0.94 (0.86 - 1.03)	0.201		
Troponin T (per 100 unit increase)	0.999 (0.977 - 1.02)	0.933		
NT - proBNP (per 100 unit increase)	1.003 (0.999 - 1.008)	0.093	1.002 (0.998 - 1.006)	0.305
Creatinine (per 50 unit increase)	1.07 (0.94 - 1.23)	0.299		

	Univariate		Multivariate	
	HR(95%CI)	P	HR(95%CI)	P
LVEF	0.99 (0.95 - 1.03)	0.605		
Right ventricular dilation	1.03 (0.25 - 4.27)	0.963		
TAPSE < 17	1.39 (0.77 - 2.50)	0.270		
FAC < 35	1.35 (0.75 - 2.44)	0.321		
RVSP	1.01 (0.99 - 1.03)	0.149	0.98 (0.95 - 1.01)	0.129
Tricuspid regurgitation severity				
Mild/Moderate	1	c	1	
Severe	1.64 (1.19 - 2.27)	**0.003**	1.94 (1.30 - 2.91)	**0.001**

The univariate regression model showed that the prognostic factor for combined events in the study patients was tricuspid regurgitation severity, with HR 1.64 (95% CI 1.19 to 2.27; p = 0.003).

The Kaplan-Meier curve in Figure 3 compared the rates of combined events (all-cause mortality and heart failure rehospitalization) in heart failure patients with reduced ejection fraction according to tricuspid regurgitation severity over 3-6 months of follow-up, showing statistically significant differences (p=0.0015). Multivariate Cox regression analysis demonstrated that tricuspid regurgitation severity was an independent prognostic factor for combined events within 3-6 months of follow-up (HR 1.94, 95% CI 1.30 - 2.91; p = 0.001).

DISCUSSION

Normally, there is a flow of blood from the superior vena cava into the right atrium throughout the systole. This flow ceases at the end of systole. The flow into the right atrium restarts at the beginning of diastole and continues until atrial contraction causes flow reversal. In people with tricuspid regurgitation, the flow into the right atrium during systole is reduced and in cases of severe regurgitation, the flow reverses from the right ventricle into the right atrium and superior vena cava. In severe tricuspid regurgitation, there are changes in right atrial compliance, reversed flow from the right ventricle into the superior vena cava continues throughout systole, and flow from the superior vena cava into the right atrium only occurs early in diastole. Sometimes, the regurgitant flow is nearly equal to the forward flow filling the right ventricle. As a result, cardiac output decreases.

Increased pressure in the right atrium leads to increased pressure in the systemic venous system and increased pressure in all organs. Chronic venous hypertension causes dysfunction of the liver, kidneys, gastrointestinal tract, brain, and many other organs.

The consequence is salt and water retention, which causes edema, pleural effusion, and ascites and can lead to multiorgan failure commonly seen in severe tricuspid regurgitation.

In our study, the rates of mild, moderate and severe tricuspid regurgitation in patients with reduced ejection fraction heart failure were 48.3%, 33.6%, and 18.1%, respectively. The Kaplan-Meier curve showed that all-cause mortality and rehospitalization at 3-6 months of follow-up were significantly higher in the severe tricuspid regurgitation group compared to the mild-moderate group (logrank p=0.0015). This is similar to the study by Koelling et al. (2002)3 of 1421 patients with reduced ejection fraction heart failure, with 1-year follow-up showing severe tricuspid regurgitation increased the risk of adverse events (p=0.001). In the study by Benfari et al. (2019), 4 of 13,026 patients with reduced ejection fraction heart failure from 2003 to 2011, more severe tricuspid regurgitation was associated with increased mortality

or hospitalization (p<0.001). According to Bartko et al. (2019), 5 in 382 patients with reduced ejection fraction heart failure, tricuspid regurgitation severity also predicted mortality and adverse events (p<0.001).

With univariate regression analysis, our study found tricuspid regurgitation severity to be a prognostic factor for combined events in patients with reduced ejection fraction heart failure. Similar results were found by Agricola et al. (2006)6 with univariate Cox regression analysis (p=0.01). After adjusting for other prognostic factors, we identified two independent risk factors for mortality and rehospitalization in patients with reduced ejection fraction heart failure: hemoglobin level and tricuspid regurgitation severity. According to the study by Bartko et al., in 382 patients with reduced ejection fraction heart failure, tricuspid regurgitation severity (HR 2.14, 95% CI 1.53-2.00; p<0.001) also had prognostic value for mortality or rehospitalization in heart failure patients.

CONCLUSION

In hospitalized patients diagnosed with heart failure with reduced ejection fraction, the severity of tricuspid regurgitation is associated with an increased risk of mortality or rehospitalization over 3-6 months of follow-up. Tricuspid regurgitation severity is an independent prognostic factor for mortality or rehospitalization in patients with heart failure with reduced ejection fraction, with a hazard ratio of 1.94 (95% confidence interval 1.30-2.91).

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