Review for RV dysfunction in ADHF

BMC Cardiovascular Ultrasound

Reviewer reports:

Reviewer #1:

In this study the authors studied the prognostic value of right ventricular dysfunction as assessed by TAPSE, and other echocardiographic and clinical comorbidities in predicting longer hospital length of stay in acute decompensated heart failure patients. The authors concluded that right ventricular dysfunction as assessed byTAPSE was an independent predictors of longer hospital hospital length of stay in acute decompensated heart failure patients patients, associated with malnutrition and worsening renal function. Since TAPSE can be easily and reliably measured in most patients, it should therefore be considered as part of routine echocardiographic examination in hospitalized ADHF patients The study is very interesting.

There are some suggestions:

1. *Please check the abbreviations (LOS in the abstract).*

Following the Reviewer's suggestion, we have replaced the position of the abbreviation of LOS (i.e. length of stay). Please check the correction on page 3 line 2.

2. *Did the authors have data about chest x-ray and chest b-lines? There are several data about correlations between chest x-ray, b-lines and right ventricular function in this subset of patients with ADHF.*

Following the Reviewer's comment, we collected chest x-ray data of all the patients. We found that 191 (73.7%) of the admitted patients had pulmonary venous congestion and interstitial edema. However, we could not find the significant association between those data with the RV function (p=0.687) nor the outcome of this study (HR 1.026; 95%CI 0.774-1.362; p=0.856). Additionally, we also analyzed the correlation between the cardio-thoracic ratio (CTR) with the RV function. Eventhough there was a statistically significant correlation, but the correlation was very weak (r=-0.175, p=0.007). Furthermore, there was no significant association between CTR with the outcome of our study (p=0.718). Accordingly, we did not put those data in the manuscript because in our opinion it won't give any additional and valuable informations.

3. *Did the authors found difference in right ventricular function (TAPSE) in ADHF patients with normal and abnormal LV systolic function (range EF 12-85%)*

We already analyzed the difference of RV function in ADHF patients based on LVEF, and we found that RV function (TAPSE) was indeed differ significantly between patients with normal and abnormal LV systolic functions (based on current ESC classification of LV dysfunction), as shown in the table below:

	LVEF < 40% (N=192)	LVEF 40 - 49% (N=27)	LVEF ≥ 50% (N=40)	p
TAPSE	1.5 (0.7 - 2.8)	1.9 (1.3 - 2.5)	2.0 (1.2 - 2.9)	< 0.001

Nevertheless, since the LVEF was not found to be an independent predictor of hospital LOS in this study, we are afraid that if we put that data in the Result, it may change the story of the paper. Therefore, we only showed it to the Reviewer.

4. The authors should explain why they have not measured the BNP and/or NT-pro BNP levels.

We absolutely agree with the Reviewer for the importance of BNP and NT-pro BNP measurements. Unfortunately, in our country, the insurance could not cover the cost of those measurements routinely. When we double checked the data, we found that only 10 (3.9%) out of 259 patients have data on NT-proBNP. Therefore, an analysis of this limited data would not represent the whole patients population. We have added this issue as one limitation of the study.

5. The authors should update references, in particular the guidelines cited (ref #19, ref #27)

Following the Reviewer suggestion, we have updated the references of the guidelined cited (ref #19 and #27).

6. The percentage of beta-blocker therapy was very low (only 46.3%, table 1). The authors should analyzed this important point.

We appreciated the critics of the Reviewer on this important issue. Unfortunately, those are the fact that we've found. The data that we showed in the table 1 was data during hospital admission. Since our hospital is the top referral hospital in the country, the patients admitted to our hospital came from various hospitals (and physicians). It is no wonder that the percentage of the beta-blocker therapy was very low (46.3%). This number was quite similar with the data from our hospital's Heart Failure Registry conducted in 2014 that showed the usage of beta-blocker therapy at admission was 41%, while the percentage at discharge increased to 68%. Unfortunately we did not have the data of our patient's medication at discharge, but based on our hospital's Heart Failure Registry, we can assume that the percentage of beta-blocker therapy at discharge would also increase.

We had also analyzed the association between heart failure medication with the outcome of the study, and none had a statistically significant association. Therefore we believe that eventhough the percentage of beta-blocker therapy was low during admission, it did not give any important effect to the hospital LOS.

Following the critic of the Reviewer, we have revised the paper on this important issue in the Result on page 9 line 10-15.

Reviewer #2:

In the present paper 259 ADHF patients admitted with ADHF were prospectively included. Clinical data and baseline right ventricular (RV) function assessed by tricuspid annular plane systolic excursion (TAPSE) at echocardiography were collected. The primary outcome was hospital length of stay (LOS): Cox regression analysis was used to identify independent predictors for longer LOS. The results show that RV dysfunction as assessed by TAPSE is an independent predictor of longer LOS, and that worsening renal function and malnutrition are also associated significantly with longer LOS.

The background of the study is interesting, as RV dysfunction has been extensively studied in stable chronic HF, however its prognostic value in the setting of ADHF patients has not yet been clarified. The methods of the study are correct: a quite large consecutive population of ADHF patients (considering that this is single center study) has been enrolled. TAPSE is a simple but useful echo indicator of RV dysfunction. Hospital LOS is a good end-point.

I have few suggestions to improve the manuscript.

1- it is of outmost importance to clarify when the "baseline" echo evaluation has been performed: was it performed in the ED? In the ward after admission? Within the first 24 hours or within the first 48 hours?

We appreciated the concern regarding this important issue from the Reviewer. All of the echocardiography examinations were performed in the ward within the first 48 hours after admission, depends on patients's clinical condition. Following this suggestion, we have put this statement in the Methods page 7 line 13-14.

2- was a second echo performed before dismission? Which changes have been observed between the first and the second echo?

Unfortunately, we did not perform second echo evaluation. Each patients included in this study only underwent a single complete echo examination, therefore we could not provide the data on the changes of echo parameters.

3- Echo data are limited to TAPSE. It is a pity. In particular I do not see echo estimate of pulmonary artery pressure. This parameter is commonly measured during the echo evaluation and it would really strengthen the study if data on pulmonary pressure and RV function could both be included in the analysis. In addition, data on inferior vena cava dilatation and collapsibility could be interesting.

We agree with the Reviewer that echocardiography data of pulmonary artery pressure was important and would strengthen the study. Therefore we already add and analyze the data of mean pulmonary artery pressure (mPAP) in the Results page 9 line 18, page 10 line 12, Table 1 and Table 2. Since the mPAP was not found to be an independent predictor of hospital LOS, we did not discuss it further on the Discussion.

We agree with the Reviewer that the addition of data on inferior vena cava dilatation and collapsibility would give better estimate of the systolic pulmonary artery pressure. We have indeed double checked the echo data, however those data were only measured in a small proportion of the patients. We are afraid that an analysis of those limited data could not stand for the actual value of the whole data. For this, we have put this as another study limitation.

4- Have the authors collected events after dismission? If so, the study would be strengthened if RV dysfunction could be related to long term survival.

We agree with the Reviewer that long-term outcome after dismission could strengthen the study (such as mortality, rehospitalization). But in this prospective study we only focus on patient's in-hospital outcome, that is the length of stay (LOS), because we believe that the LOS is one of the important clinical outcomes that determines higher morbidity and hospitalization cost in ADHF patients (as already stated in the study background).

5- Rather than excluding patients with tricuspid regurgitation, we would include "severe TR" as a covariate in statistical analysis.

We actually did not exclude all patients with tricuspid regurgitation (TR). Only patients with severe TR were not included in the study because the accuracy of TAPSE value has not been established in those patients. These two papers explained this issue:

1. Hsiao SH, Lin SK, Wang WC et al. Journal of the American Society of Echocardiography. 2006;19:902-10 :'…although measurement of tricuspid annular motion seems to provide an appealing, uncomplicated approach to determine RV systolic function, its accuracy in severe TR is disappointing.'
2. Howard LS, Grapsa J, Dawson D. et al. European Respiratory Review 2012;21:239-48 : 'A significant limitation of TAPSE is that it is highly load dependent, such that it may become pseudonormalised in the presence of significant volume loading, e.g. left-to-right shunting or severe functional tricuspid regurgitation.'

Therefore, in our opinion, it is not appropriate to put severe TR as a covariate.

6- If no data are available on long term follow up and no other echo data are available, these should be acknowledged as Study Limitations.

As we mentioned to the answer no 4, we agree that data on long term outcomes (e.g. mortality, rehospitalization) would give additional values to this study. However, the prognostic values of RV dysfunction to predict mortality and rehospitalization in ADHF patients have been published elsewhere, e.g.:

1. Ghio S, Temporelli PL, Klersy C, et al. Prognostic relevance of a non-invasive evaluation of right ventricular function and pulmonary artery pressure in patients with chronic heart failure. European Journal of Heart Failure 2013;15:408-14.
2. Damy T, Kallvikbacka-Bennett A, Goode K, et al. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. Journal of Cardiac Failure 2012;18:216-25.
3. Kjaergaard J, Akkan D, Iversen KK, Kober L, Torp-Pedersen C, Hassager C. Right ventricular dysfunction as an independent predictor of short- and long-term mortality in patients with heart failure. European Journal of Heart Failure 2007;9:610-6.

In this paper, we focus on the clinical outcome of hospital LOS, and the fact the we found the prognostic value of TAPSE in the prediction of LOS in ADHF patients is one important novelty of this study.

Regarding data on echo, we have added data on the mean pulmonary artery pressure in the Results. We agreed to put the lack of data on inferior vena cava dilatation and collapsibility in the Study Limitations page 13 line 10.