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ORIGINAL ARTICLE

Biohumoral markers as predictor of right ventricular dysfunction in AL Amyloidosis

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Abstract

Aim: In AL amyloidosis, the importance of right ventricle (RV) involvement has recently been underlined and its role in predicting prognosis has been emphasized. Little is known about the relationship between RV involvement, N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin levels. Aim of our study was to clarify the relationship between NT-proBNP and troponin and RV involvement and analyze their independent value as predictors of RV dysfunction.

Methods and Results: We examined 76 consecutive patients with biopsy-proven AL amyloidosis. Each patient received complete clinical evaluation, troponin I, NT-proBNP assay and comprehensive echocardiographic evaluation. Considering a tricuspidal annulus plane systolic excursion (TAPSE) value <16 mm, 23 patients (30%) presented RV systolic dysfunction, whereas 53 (70%) did not. Patient with reduced TAPSE had thicker left ventricle (LV) walls and RV free walls, reduced LV fractional shortening, impaired LV diastolic function and worse LV and RV myocardial performance index. For RV dysfunction the best predictive value for NT-proBNP was identified as 2977 ng/l with sensitivity and specificity of 87% and 84%, respectively; best cut-off for troponin I was identified as 0.085 ng/l, with sensitivity and specificity of 85% and 90% respectively.

At multivariable logistic regression analysis, both NT-proBNP and troponin I emerged as independent predictors of RV dysfunction presence but troponin appears to have a higher predictive power.

Conclusion: Our study demonstrated that cut-off values of 2977 ng/ml for NT-proBNP and 0.085 ng/l for troponin were able to identify a subgroup of AL patients with RV dysfunction. Troponin I is more accurate and seems to be the best biohumoral marker of RV dysfunction.

Abbreviations: BSA: body surface area; DT: E wave deceleration time; EF: LV ejection fraction; FLC: free light chain; FS: LV fractional shortening; IVS: end-diastolic thickness of interventricular septum; LV: left ventricular; LV EDD and LV ESD: LV end-diastolic and end-systolic diameters respectively; LV EDV and LV ESV: LV end-diastolic and end-systolic volumes respectively; MPI: myocardial performance index; MDRD: modification of diet renal disease; NT-proBNP: N-terminal pro-brain natriuretic peptide; PASP: pulmonary artery systolic pressure; PW: LV posterior wall; RV: right ventricle; RV EDD: RV end diastolic diameter; TAPSE: tricuspidal annulus plane systolic excursion; TDI: tissue Doppler imaging

Keywords

AL amyloidosis, NT-proBNP, right ventricular dysfunction, troponin

History

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Introduction

Amyloidosis is a rare systemic disease characterized by extracellular deposition of protein derived fibrils in various tissues and organs, including the heart [1–2]. Cardiac involvement usually determines prognosis and, among the different forms of cardiac amyloidosis, Amyloid Light-chain (AL) has the worse outcome [3]. Since the hallmark of cardiac amyloidosis is a restrictive cardiomyopathy, medical attention has been focused traditionally on left ventricular (LV) diastolic function. However, in the last few years, due to the availability of more advanced echocardiographic techniques, such as tissue Doppler imaging (TDI) and 2-dimensional speckle tracking echocardiography, consideration has been given to the study of geometrical modification of LV systolic

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function [4–6]. In addition, the involvement of the right ventricle (RV) and its role in predicting prognosis in AL amyloidosis has recently been emphasized [7–8]. Since the seminal work of Paladini et al. [9], N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin have been employed in AL amyloidosis for diagnosis of cardiac involvement and prognostic evaluation [10]. Although several studies have proven the relationship between cardiac biomarkers and RV dysfunction in patients with acute pulmonary embolism and arterial pulmonary hypertension [11,12], comparison among those cardiac biomarkers in the prediction of RV dysfunction and their optimal cutoff values in patients with cardiac AL amyloidosis were poorly investigated.

So the aims of our study were (1) to clarify the relationship between NT-proBNP and troponin and RV involvement (2) to analyze the independent value of NT-proBNP and troponin as indicators of RV dysfunction and identify the best cut off values.

Material and methods

Seventy-six consecutive patients (43 females and 33 males, mean age 69.5 ± 9.8 years) with biopsy-proven AL amyloidosis were examined at the Tuscan Regional Centre of Amyloidosis, Florence (Italy), between February, 2007, and December, 2012. All participants gave informed written consent, following the Helsinki declaration. Positive biopsy site was abdominal fat in 52 patients (68%), kidney in 12 (17%), myocardium in 4 (5%), salivary gland in 3 (4%), bone marrow in 2 (3%), stomach, lymph node and liver in 1 patient (1%). All positive biopsies demonstrated the typical Congo red birefringence under polarized light. According to international criteria [13], AL amyloidosis was confirmed by the finding of a monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow by immunohistochemistry. All participants underwent a thorough medical history and a complete clinical evaluation. Hereditary amyloidosis was excluded by DNA analysis in all patients.

NT-proBNP was measured with an electro-chemiluminescence sandwich immunoassay (ECLIA, Roche Diagnostic, Indianapolis, IN) in the central hospital laboratory. Troponin I measurements were performed by immuno-chemiluminescence assay using a Centaur XP (Siemens Healthcare, Erlangen, Germany). Serum free light chains (FLC) were determined using the Freelite assay (Binding Site, Birmingham, United Kingdom). Creatinine clearance using modification of diet renal disease (MDRD) formula [14] and both systolic and diastolic arterial blood pressure were evaluated.

Standard and TDI echocardiography

At the time of diagnosis patients were referred to our laboratory for M-mode, 2-dimensional, conventional and tissue Doppler echocardiographic study [15]. Echocardiography was performed by a single experienced operator (FC), blinded to the clinical history of the patient, using a Vivid 7 System (Vingmed, General Electric, Horten, Norway) equipped with a 3S probe. At least three consecutive beats were recorded and the images were digitized and analyzed off-line. The following parameters were assessed: end-diastolic thickness of interventricular septum (IVS) and LV posterior wall (PW), LV end-diastolic and end-systolic diameters (LV EDD and LV ESD, respectively), body surface area (BSA)-indexed LV mass ($LVmass_{ind}$), LV endocardial fractional shortening (FS), left atrial area (LAA, evaluated from the apical four chamber view at the end of systole), LV end-diastolic and end-systolic volumes (LV EDV and LV ESV, respectively), ejection fraction (EF, estimated with the biplane Simpson method), mitral peak flow velocity in early and late diastole (E and A, respectively, during atrial contraction), E wave deceleration time (DT), E/A ratio, LV and RV myocardial performance index (MPI, the sum of isovolumic contraction and relaxation times divided by ejection time, as previously described [16]), RV free wall thickness (RV FW), RV end-diastolic diameter (RV EDD, evaluated from parasternal long axis view) and the systolic displacement of the lateral portion of the tricuspid annular plane (TAPSE).

Pulmonary artery systolic pressure (PASP) was approximated by adding to trans-tricuspid pressure gradient an estimate of right atrial pressure. We also evaluated pulsed TDI-derived early diastolic peak velocity at mitral annulus (E'), as an index of LV relaxation, and E/E' ratio as an index of LV filling pressure. According to the literature, patients were classified as having RV dysfunction when TAPSE value was <16 mm [17].

Statistical analysis

Statistical analysis was conducted using the SPSS® for Windows package version 13 (SPSS Inc., Chicago, IL). Categorical and continuous variables were expressed as frequencies (percentages) and as mean ± standard deviation, respectively. Categorical comparisons were performed with Pearson Chi square and one factor analysis of variance (ANOVA) was used for comparison between groups. Area under the receiver operating characteristics curve (ROC) analysis was used to determine the optimal cutoff of troponin and NT-proBNP as markers of RV dysfunction; sensitivity, specificity, positive and negative predicted value were computed. Among variables that had an independent predictive value on the presence or absence of RV dysfunction at univariate analysis, but with similar clinical significance, only one was introduced in the multivariate logistic regression model, to avoid co-linearity. On this basis we tested three different multivariable logistic models in which NT-proBNP (Model 1), troponin I (Model 2) e NT-proBNP + troponin I (Model 3) were introduced as independent variables. A p value less than 0.05 was considered statistically significant.

Results

Clinical and echocardiographic characteristics of the study population are reported in Tables 1 and 2. According to a TAPSE value <16 mm, 23 patients (30%) were classified as having a RV systolic dysfunction; 53 (70%) had a normal RV function. As reported in Table 1, no differences were observed between normal and dysfunctional patients in terms of age, gender, eGFR and number of AL amyloidosis involved organs. The prevalence of a history of diabetes mellitus, arterial hypertension, coronary artery disease and peripheral artery disease did not differ between the groups (48% in

Table 1. Demographic. clinical and biohumoral characteristics.

	All patients	TAPSE ≥16 mm ($n=53$)	TAPSE <16 mm ($n=23$)	p Value
Age (years)	69.5 ± 9.8	68.9 ± 10.1	70.7 ± 9.2	0.49
Gender (M/F)	33/43	24/29	9/14	0.61
BSA (m^2)	1.7 ± 0.3	1.7 ± 0.3	1.6 ± 0.4	0.53
eGFR (ml/min)	58.7 ± 26.5	58.3 ± 28.4	59.8 ± 21.7	0.83
Arterial diastolic pressure (mm/Hg)	69 ± 11	70 ± 9	69 ± 10	0.18
Arterial sistolic pressure (mm/Hg)	117 ± 16	119 ± 16	115 ± 19	0.12
NT-proBNP(ng/l)	5177.6 ± 9113	2132 ± 4972	11797 ± 12240	0.001
Troponin I(ng/)	0.12 ± .21	0.039 ± .035	0.28 ± .31	0.001
Free light K/λ %	23/53	20/33	3/20	0.06
NYHA Class				
I–II	60	49	11	0.0001
III–IV	16	4	12	
Number of involved organs				
I	45	33	12	0.43
II	21	12	9	
III	6	5	1	
IV	4	2	2	

Table 2. Echocardiographic characteristic of studied population.

	All patients	TAPSE ≥16 mm ($n=53$)	TAPSE <16 mm ($n=23$)	p Value
LVDD (mm)	44.8 ± 6.1	45.5 ± 4.8	43 ± 8.2	0.14
LVSD (mm)	27.6 ± 5.8	26.9 ± 5.3	29.3 ± 6.8	0.1
FS %	38.3 ± 8.8	40.9 ± 8.4	32.4 ± 6.7	0.0001
IVS (mm)	12.9 ± .2	11.5 ± 2	16.3 ± 3.1	0.0001
PW (mm)	12.8 ± 3.0	11.5 ± 2.3	15.7 ± 2.3	0.0001
LV mass index (g/m^2)	131.3 ± 3.1	113 ± 33	171 ± 36	0.0001
RV FW (mm)	6.4 ± 1.3	5.9 ± 1.2	7.4 ± 0.7	0.0001
RVDD (mm)	28.3 ± 6.5	27.3 ± 6.4	30.3 ± 6.5	0.07
LVEDV (ml)	80.2 ± 23.8	83.5 ± 19.9	72.8 ± 29.9	0.07
LVESV (ml)	33.1 ± 14	33.6 ± 12.8	31.7 ± 16.5	0.58
EF (%)	59 ± 8.5	59.9 ± 8.3	56.9 ± 8.9	0.16
LA area (cm^2)	20.9 ± 4.6	19.3 ± 3.9	24.4 ± 4.3	0.0001
Mitral Regurgitation mild -moderate/Severe	66/10	50/3	16/7	0.003
E (cm/s)	74.9 ± 20.2	72.4 ± 18.6	80.5 ± 22.8	0.11
A (cm/s)	69.8 ± 27.0	78.6 ± 24.7	49.1 ± 20.5	0.0001
E/A	1.3 ± .83	1 ± 0.6	1.9 ± 0.9	0.0001
DT (ms)	207 ± 76	219 ± 75	180 ± 74	0.045
E' (cm/s)	5.8 ± 2	6.5 ± 2	4.4 ± 1.1	0.0001
E/E'	14.3 ± 7	12 ± 5.3	19.3 ± 7.9	0.0001
LV MPI	0.46 ± .20	0.38 ± 0.15	0.63 ± 0.19	0.0001
PASP (mm/Hg)	33.2 ± 11.8	28.5 ± 9.7	41.5 ± 10.9	0.0001
RV MPI	0.39 ± .23	0.34 ± 0.16	0.48 ± 0.3	0.04

LV: left ventricular; RV: right ventricular; IVS: interventricular septum thickness; PW: posterior wall thickness; RWFW: RV free wall thickness, RVDD: RV end diastolic diameter LVEDD: LV end-diastolic diameter; LVESD: LV end-systolic diameter; FS: Fractional Shortening; LA: Left Atrium; LVEDV: LV end-diastolic volume LVESV: LV end-systolic volume; EF: Ejection Fraction; E: early diastolic mitral peak flow velocity; A: late diastolic mitral peak flow velocity; E': early diastolic peak velocity at lateral mitral annulus; MPI: Myocardial performance index; PASP: pulmonary artery systolic pressure; TAPSE: Tricuspid annular plane systolic excursion

patients with RV systolic dysfunction and 51% in patient without RV systolic dysfunction). Patients with reduced RV function had more frequent heart failure symptoms and higher New York Heart Association (NYHA) class; they also had higher NT-proBNP and troponin I plasma values.

Patients with reduced TAPSE had thicker LV PW, higher LV $mass_{ind}$, reduced FS and worse LV MPI. No significant differences in LV systolic and diastolic volumes and diameters were found while atrial area was significantly larger in patients with RV dysfunction (Table 2). As for diastolic function, patients with RV dysfunction showed lower A velocity and higher E/A ratio, with significantly reduced E' and increased E/E' ratio. E velocity and DT were similar between groups. Patients with reduced TAPSE had thicker RV FW with comparable RV EDD, enhanced RV MPI and a significant increase in PASP.

Biohumoral predictors of RV dysfunction

As reported in Figure 1(A), the best predictive value for NT-proBNP was 2977 ng/l, with an area under the curve of 0.90 ($p<0.0001$) and a sensitivity and specificity of 87% and 84%, respectively. Using the prevalence of RV involvement observed in our cohort (35%), the positive and negative

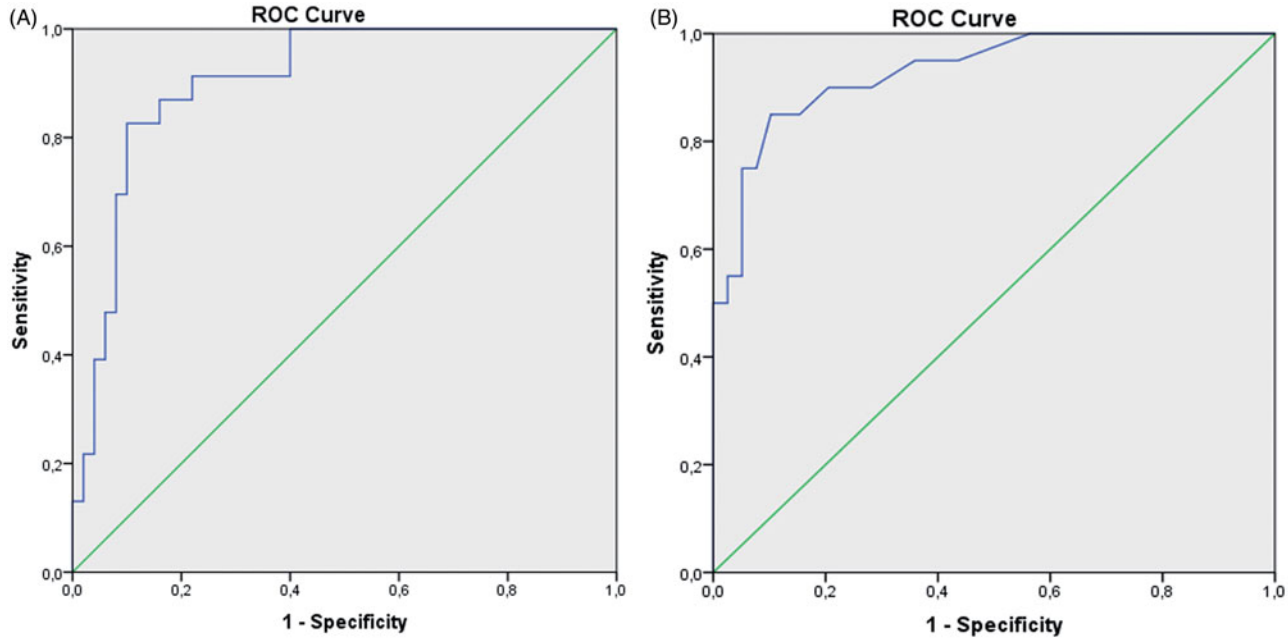

Figure 1. (A) The receiver-operator characteristic analysis for the study population indicated that NT-proBNP with a cut off value of 2977 ng/l reached a sensitivity of 87% and specificity of 84% in detecting right ventricular dysfunction AUC 0.90 $p < 0.0001$. (B) The receiver-operator characteristic analysis for the study population indicated that Troponin I with a cut off value of 0.085 ng/l reached a sensitivity of 85% and specificity of 90% in detecting right ventricular dysfunction AUC 0.93 $p < 0.0001$.

Table 3. Multivariable logistic regression analysis models.

	Model 1			Model 2			Model 3		
	B ± SE	Wald	*p*	B ± SE	Wald	*p*	B ± SE	Wald	*p*
Age	0.04 ± 0.04	1.1	0.28	0.20 ± 0.10	3.77	0.06	0.19 ± 0.11	2.8	0.09
NYHA Class	0.66 ± 1	0.4	0.52	0.6 ± 3.2	1.6	0.2	0.6 ± 3.2	0.04	0.85
LV mass index	0.036 ± 0.013	10.2	0.001	0.06 ± 0.03	4.3	0.04	0.06 ± 0.03	4.3	0.04
FS%	−0.07 ± 0.05	2	0.15	−0.08 ± 0.09	0.76	0.38	−0.83 ± 0.09	0.76	0.38
Mitral Regurgition	−1.75 ± 0.9	3.6	0.06	−3.5 ± 1.7	3.95	0.05	−3.5 ± 1.7	3.9	0.05
E/E'	0.06 ± 0.07	0.89	0.34	0.13 ± 0.14	0.84	0.35	0.13 ± 0.14	0.84	0.35
NT-proBNP	0.001 ± 0.001	3.92	0.04				0.001 ± 0.001	0.22	0.8
Troponin I				98.3 ± 46	4.46	0.03	98 ± 46	4.4	0.03

predictive values were 62.5% and 97.5%, respectively. Troponin I best cut-off was 0.085 ng/l with an area under the curve of 0.93 ($p < 0.0001$), a sensitivity of 85% and a specificity of 90% (Figure 1B); positive and negative predictive values were 75% and 88.2%, respectively.

Nine patients showed NT-proBNP concentrations above the cut-off value (2977 ng/l) but did not exhibit RV dysfunction (false positive); four of them also had troponin I serum levels above 0.085 ng/l. Eight out of nine had high serum creatinine levels with MDRD lower than 50 ml/min. The results of the three multivariable logistic models are reported in Table 3: both NT-proBNP and troponin I emerged as independent predictors of RV dysfunction (Model 1 and Model 2), with troponin I being the strongest predictor (Model 3).

Discussion

We studied and compared the predictive value of two commonly used cardiac biomarkers, NT-proBNP and troponin I, in evaluating the presence of RV dysfunction, as determined by echocardiography, in AL cardiac amyloidosis patients. We found that troponin I showed a better sensitivity and specificity than NT-proBNP.

Several reports have demonstrated that circulating NT-proBNP and troponin are valuable markers of cardiac involvement in AL amyloidosis and are predictors of overall survival [9, 18–21]. The clinical contribution of RV dysfunction in AL cardiac amyloidosis has been emphasized previously [7,8,22]. At present, echocardiography remains the best method for the study of RV function and a dysfunctional RV, assessed by different echocardiographic techniques, is an independent, useful predictor of mortality in cardiac AL amyloidosis patients [7,8,22,23].

Recently, our group demonstrated that a mean RV longitudinal 2D speckle-tracking strain less than −17% identifies a subgroup of cardiac AL amyloidosis patients with marked RV dysfunction and high risk of death [8]. In addition, at multivariate analysis, RV longitudinal strain was the only echocardiographic predictor of prognosis [8]. These data were in agreement to what was reported by Ghio and coworkers that identified TAPSE as a marker

of RV systolic dysfunction and a predictor of poor prognosis [18].

Thus, an early identification of RV dysfunction in such patients might provide therapeutic guidance because such patients need rapidly active treatment but at the same time they are extremely fragile and sensitive to treatment toxicity. Despite the fact that echocardiographic evaluation of RV function, as with TAPSE, is feasible even with low technology, widespread echocardiographic equipments, determining NT-proBNP and troponin I serum concentrations could be even easier in every day clinical practice. However, in order to do that, the best cut-off values of the two biomarkers need to be determined. To our knowledge this is the first study that attempted to answer this question.

Using a cohort of patients with cardiac AL amyloidosis we found that both NT-proBNP and troponin I was able to predict RV involvement. Interestingly, in our cohort the value of NT-proBNP and troponin I was, on average, higher than what was previously reported to be correlated with a generic ''amyloid heart involvement'' [9,10,20].

Indeed, the best predictive value of NT-proBNP for RV amyloid dysfunction was 2977 ng/l which was above the mean value usually indicative of overt heart failure [24]. However, amyloidosis is an infiltrative disease that affects both ventricles walls and which exerts its deleterious effects on the heart also through a direct toxic action of the amyloidogenic free light chains. We can speculate that this high cut off value could be the consequence of LV dysfunction and direct RV infiltration as suggested by increased RV free wall thickness.

These data also confirms the previous observations that in AL amyloidosis patients, RV dysfunction occurs later than LV, with a more advanced disease and, more often, with the presence of overt heart failure [8,22]. In fact, our results show that patients with reduced TAPSE present thicker LV walls, enlarged left atria, more compromised LV diastolic function with increased left atrium filling pressure. Furthermore, they present more frequently significant mitral regurgitation, increased pulmonary artery pressure and advanced NYHA class.

Nevertheless our data also shows that troponin ($\geq$0.085 ng/l), rather than NT-proBNP, has the best specificity and sensitivity in predicting RV dysfunction. However, the interpretation of those results may be misleading. Indeed, it should be kept in mind that NT-proBNP is almost exclusively removed through glomerular filtration and, therefore, renal insufficiency may lead to an additional increase of the peptide that is not to be attributed to amyloid heart involvement. Among the nine patients with NT-proBNP levels above the cut-off value of 2977 ng/l, but without echocardiographic signs of RV dysfunction, eight showed high serum creatinine levels, with MDRD eGFR under the value of 50 ml/min. Higher NT-proBNP cut-off values are probably required to identify RV dysfunction in amyloid patients with decreased eGFR [25]. On the other hand, only four patients without echocardiographic evidence of RV dysfunction showed troponin I serum levels above the cut-off value of 0.085 ng/l, suggesting that this biomarker could be less influenced by the simultaneous presence of renal failure.

In AL amyloidosis, increased troponin I levels have been attributed to cardiac injury which could be mediated by several mechanisms, including microvascular coronary ischemia, mechanical effects of amyloid infiltration, and/or direct toxic effect of amyloid proteins and their precursors [26]. A recent study by Sied and coworkers demonstrated that global late gadolinium enhancement on cardiac magnetic resonance in patients with amyloidosis was associated with increased circulating troponin levels, suggesting a correlation of this biomarker with a more advanced stage of infiltration [27]. Therefore, the best performance of troponin I in predicting RV dysfunction could be explained by the fact that it is a marker of more diffused heart involvement.

Study limitations

The study presents all limitations of a cross-sectional design. Due to the small number of patients our observations must be considered preliminary and need to be confirmed in larger, prospective longitudinal trials that could explore further the relationship between NT-proBNP and troponin increase and the onset of RV dysfunction. The troponin assays are multiple, addressing either circulating troponin I or T, with different sensitivity levels and with different imprecision levels. This could make the cut-off point proposed in the present study strictly associated with our series.

Conclusion

Our study demonstrates, for the first time, that a cut-off value of 2977 ng/ml for NT-proBNP and of 0.085 ng/l for troponin I are able to identify a subgroup of AL amyloidosis patients with RV dysfunction. Troponin I demonstrate better accuracy and proves to be the best biohumoral marker of RV involvement. Based on the results of the present study it is expected that simple measurements of cardiac biomarkers could easily and quite accurately suggest the presence of RV dysfunction, even when an accurate echocardiographic evaluation of right ventricular function is not feasible for anatomical or technical reason.

Declaration of interest

The authors report no conflicts of interest.

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