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Prevalence and evolution of right ventricular dysfunction among different genetic backgrounds in dilated cardiomyopathy

Short title: RVD in genetically determined DCM

Paolo Manca, MD[1], Antonio Cannatà, MD[1-2], Vincenzo Nuzzi, MD[1], Daniel I. Bromage[2], Guerino Giuseppe Varrà, MD[1], Maddalena Rossi, MD[1], Matteo Dal Ferro, MD[1], Alessia Paldino, MD[1], Marta Gigli, MD[1], Giulia Barbati[3], Federica Ramani [1], Bruno Pinamonti, MD[1], Davide Stolfo, MD[1-4], Maurizio Porcu, MD,FESC[5], Luisa Mestroni, MD,FACC[6], Marco Merlo, MD[1], Gianfranco Sinagra, MD,FESC[1].

[1] Department of Cardiology, Azienda Sanitaria Universitaria Integrata Giuliano Isontina (ASUGI), University of Trieste, Trieste, Italy.

[2] Department of Cardiovascular Science, Faculty of Life Science and Medicine, King's College London, London, UK.

[3] Biostatistics Unit, University of Trieste, 34100 Trieste, Italy.

[4] Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

[5] Department of Cardiology, Azienda Ospedaliera Brotzu, Cagliari, Italy.

[6] Cardiovascular Institute, University of Colorado Anschutz Medical Campus, Aurora.

Corresponding Author:

Marco Merlo, MD, Division of Cardiology, Cardiovascular Department, Azienda Sanitaria Universitaria Integrata Giuliana Isontina (ASUGI), University of Trieste, Trieste, Italy Via Valdoni 7, 34149 - Trieste, Italy. Tel: +390403994477; fax: +390403994153. E-mail: marco.merlo79@gmail.com.

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Abstract (250/250 words)

Background: Titin (*TTN*) related dilated cardiomyopathy (DCM) has a higher likelihood of left ventricular reverse remodeling (LVRR) compared to other genetic etiologies. No data regarding the evolution of right ventricular dysfunction (RVD) according to genetic background is available.

Methods: Consecutive 104 DCM patients with confirmed pathogenic genetic variants (51 *TTN* related DCM; 53 other genetic DCM) and a control group of 139 patients with negative genetic testing and available follow-up data at 12-24 months were analyzed. RVD was defined as a right ventricular fractional area change (RVFAC) <35%. The main study end-point was the comparison of the evolution of RVD and the delta change of RVFAC throughout the follow-up according to etiology. A composite of all-cause mortality and heart transplantation was included as outcome measure.

Results: At enrolment, RVD was present in 29.1% of genetically positive DCM without differences between genetic cohorts. At 14 months follow-up, 5.9% of *TTN* related DCM patients vs. 35.8% of other genetic DCM patients had residual RVD after treatment (p <0.001). Accordingly, RVFAC significantly improved in the *TTN* related DCM cohort remaining stably impaired in other genetic DCM patients. However, the evolution of RVD was comparable between *TTN* related DCM and patients without a genetic mutation. After adjusting for RVD at follow-up, no differences in the outcome measure were seen in the study cohorts.

Conclusions: The evolution of RVD in DCM is heterogeneous in different genetic backgrounds. *TTN* related DCM is associated with a higher chance of RVD recovery compared to other genetic etiologies.

Keywords: Right ventricular dysfunction, Dilated Cardiomyopathy, Genetics, Titin.

Brief Summary

Right ventricular dysfunction is present in approximately 30% of patients with dilated cardiomyopathy (DCM) at the first clinical presentation, regardless of their genetic background. We observed that most of patients with *TTN* related DCM or without an identifiable genetic background recover their right ventricular function during the first 14 months of guideline-directed medical treatment. However, other genetic etiologies are associated with persistent RVD, probably reflecting a biventricular involvement of the disease.

Introduction

Dilated cardiomyopathy (DCM) is a primary heart muscle disease defined by left- or bi-ventricular systolic dysfunction in the absence of abnormal loading conditions or significant coronary artery disease [1;2]. A specific genetic background is identified in up to 40% of DCM patients, with 40 to 60 causative genes involved in determining the clinical phenotype [3;4]. Among these, truncating variants in the titin (*TTN*) gene represent the most prevalent etiology, accounting for 11 to 25% of genetically determined DCM [4].

Recently, considerable efforts have been devoted to characterizing the clinical phenotype of *TTN* related DCM. Evidence suggests that *TTN* truncating variants are associated with milder forms of DCM and a higher likelihood left ventricular reverse remodeling (LVRR) with guideline-directed medical treatment (GMT) [5-7].

So far, no data are available about the prevalence and evolution of right ventricular (RV) involvement in patients affected by *TTN* related DCM. Right ventricular dysfunction (RVD) is identifiable in approximately 30% of DCM patients at the initial clinical presentation [8;9], with a

high rate of RVD recovery following 6-12 months of GMT [10]. However, differences in the prevalence and progression of RVD according to genetic background have not been explored.

The aim of this study was to assess the prevalence and evolution of RVD in patients with *TTN* related DCM compared to other pathogenic genetic variants and DCM patients with no genetic determinants.

Methods

Inclusion and exclusion criteria

All consecutive patients enrolled to the Trieste Heart Muscle Disease Registry, Italy [11], from January 1995 to December 2017, were screened for inclusion. Patients with an available genetic test documenting a pathogenic or likely pathogenic mutation and available follow-up data at 12-24 months were eligible. A control group of genetically tested DCM patients enrolled in the same time-frame, in which genetic testing was either negative or demonstrated a variant of uncertain significance, was also included. The enrolment was considered the first evaluation in our Center.

DCM was defined as left ventricular ejection fraction (LVEF) <50% in the absence of a history of significant hypertension, > 50% stenosis of a major epicardial artery, excessive alcohol intake, chemotherapy, advanced systemic disease affecting short-term prognosis, pericardial diseases, congenital heart diseases, cor pulmonale, persistent supraventricular tachyarrhythmias, or active myocarditis [1;2]. Furthermore, as previously reported [12], all patients fulfilling criteria for “definite”, “probable” or “possible” of arrhythmogenic right ventricular cardiomyopathy (ARVC) (with the exception of desmosomal mutation carrier status) were also excluded [13].

The presence of coronary artery disease was ruled out by coronary artery angiography or computed tomography. Endomyocardial biopsy was performed in patients with suspected active myocarditis.

All patients were on GMT, unless contraindicated or not tolerated [14], and received implanted cardioverter defibrillators (ICDs) and/or cardiac resynchronization therapy (CRT) according to international guidelines [15].

Echocardiographic analysis

LV and RV dimensions and function were assessed according to international guidelines [16]. LV volumes and diameters were indexed according to patients' body surface area. LVEF was calculated by Simpson's biplane method.

RVD was considered as RV fractional area change (RVFAC) ([end-diastolic area–end-systolic area]/end-diastolic area x 100) <35%. Changes in RV function from baseline to follow-up were assessed.

Left ventricular reverse remodeling (LVRR) was defined by an absolute increase in LVEF ≥10% (or absolute LVEF at follow-up ≥50%), associated with a relative reduction in indexed left ventricular end-diastolic diameter ≥10% (or absolute value at follow-up ≤33mm/m^2) [17].

Mitral regurgitation (MR) was considered significant only if moderate to severe (grade 2 – 4).

Genetic analysis and cluster Classification

Using Next-Generation Sequencing (NGS), patients' blood samples were tested for cardiomyopathy-related genes. The genetic testing covered more than 95% of known DCM related genes, which has been previously reported [12]. All patients were sequenced (see supplementary material for more details on the genetic panel used). All variants were validated with bidirectional

Sanger sequencing and were classified according to current guidelines [18]. The minor allele frequency (MAF) was verified in the gnomAD (https://gnomad.broadinstitute.org/variant/22-46449891-G-A) and crosschecked with the ClinVar (http://www. ncbi. nlm. nih. gov/ clinvar) and CardioClassifier (https://www.cardioclassifier.org/) databases.

Patients with rare variants in genes belonging to the same subcellular compartment or with similar functions were clustered in different groups, as previously described [7].

Based on the genetic test results, patients were divided into two groups: *TTN* related DCM and other genetic DCM.

Study endpoint and outcome measure

The primary endpoint was the change throughout of RVFAC and the different prevalence of RVD from baseline to follow-up revaluation between *TTN* related DCM and other genetic DCM patients. A subsequent analysis conducted in the genetically tested negative DCM patients was also included and compared to the two main cohorts.

A composite of all-cause mortality and heart transplantation (HTx) was also included as an outcome measure. Outcome data was obtained directly from the patient, their general physician, or from the registers of death of the municipalities of residence.

The study was approved by the ethics committee (Ethical approval 43/2009) and performed according to the Helsinki declaration. All patients gave written informed consent.

Statistical analysis

Clinical and laboratory variables were expressed as mean and SD, median and interquartile ranges (IQR), or as counts and percentages, as appropriate. Cross-sectional comparisons between groups were made by the analysis of variance test on continuous variables, using the Brown-Forsythe statistic when the assumption of equal variances did not hold, or the non-parametric median test when necessary. Chi-square or Fisher exact tests were calculated for categorical variables. For binary variables, the McNemar test was calculated. Paired sample T-tests were performed to assess the evolution of RVFAC in the different cohorts. Univariable logistic regression was performed to assess the baseline parameters associated with the maintenance or incidence of RV dysfunction at follow-up. A multivariable model including the variables with p-value <0.1 at the univariable analysis [19] was performed. Due to the low number of events, other two multivariable models were built and the AUC of the models was compared with a ROC curve. A Kaplan-Meier curve for all-cause mortality and HTx was used to compare patients according to their genetic background. Cox regression analysis was performed to assess the role of genetic background and RVD at follow-up in determining the outcome measure. In the main analysis familial cases were included. A sensitivity analysis considering only probands was performed. Inter-observer and intra-observer variability in RVFAC measurement was ascertained by randomly selecting a sample of 40 patients with DCM. Two different operators (P.M. and V.N.) performed a double evaluation to achieve 90% power and, thus, to detect an intraclass correlation (ICC) of 0.8 under the null hypothesis of ICC = 0.6, by using an F-test with a significance level of 0.05. The Kappa agreement was also computed for both RVFAC and RVD as binary parameters. IBM SPSS software version 24 (IBM, Armonk, New York) and the R statistical software (library “cmprisk”) were used for the analysis.

Results

Study population

We identified 139 patients with a genetically determined DCM. Of these, 32 patients with missing echocardiographic data in the follow-up period, or where RVFAC could not be estimated due to poor echocardiographic windows, were excluded. Moreover, 3 patients (1 in the *TTN* related DCM cohort and 2 in the other genetic DCM group) died prior to the follow-up evaluation. A final cohort of 104 patients (51 were affected by *TTN* related DCM (49%) and 53 had another genetic etiology (51%) constituted the study population (Supplementary table S1 and Supplementary figure S1).

The baseline characteristics of the study population are illustrated in table 1. Patients were predominantly males, and those affected by *TTN* related DCM were older compared to those with other genetic DCM (47±14 vs 37±15 years old, respectively; p=0.002). Generally, patients had recent onset of heart failure (HF) (1 [IQR 0-8] months) without differences between the groups, and severely depressed LVEF. After a median follow-up of 14 [IQR 10-18] months, significantly more patients in the *TTN* related DCM group achieved LVRR compared to the other genetic DCM patients (37.2% vs 18.9%; p=0.049; table 2 and Supplementary table S2).

Prevalence and evolution of right ventricular dysfunction according to genetic background

At baseline, RVFAC was significantly higher among *TTN* related DCM patients (42±11% vs 35±11%; p=0.011), despite a non-significant difference in the prevalence of RVD in the two groups (21.6% vs 35.8%; p=0.132) (table 1).

At follow-up, RVFAC significantly improved in the *TTN* related DCM cohort (from 42±11% to 46±7%; p=0.023), while it remained almost unchanged in patients affected by other genetic DCM (from 35±11% to 36±10%; p=0.340). Moreover, the prevalence of RVD at follow-up significantly differed

in the study groups (5.9% vs 35.8% in *TTN* related DCM vs other genetic DCM, respectively; p<0.001), with a clear reduction of RVD prevalence in the *TTN* related DCM group (from 21.6% to 5.9%) and no differences between baseline and follow-up in the other cohort (from 35.8% to 35.8%) (table 2 and figure 1).

Predictors of right ventricular dysfunction at follow-up

After adjusting the model for the most relevant clinical variables with an a-priori selection (i.e. *TTN* related DCM vs other genetic DCM, baseline LVEF and RVD), genetic background different from *TTN* variants (OR 16.458; 95% C.I. 3.095-87.513, p=0.001) and the presence of baseline RVD (OR 6.776; 95% C.I. 1.976-23.239, p=0.002) independently predicted the persistence of RVD (table 3). As a sensitivity analysis, two other models were built. Model 2 considered LAESA instead of LVEF, while model 3 was mildly overfitted and included all the significant clinical variables at univariable analysis (Supplementary table S3). In both models, both baseline RVD and the genetic background remained independently associated with RVD at follow-up (Supplementary table S4). There were no significant differences in the AUC of any of the models (Supplementary figure S2).

Outcome measure

At a median follow up of 97 months [IQR 48-160], 3 of the 51 patients of the *TTN* group (5.9%) and 16 of the 53 patients of the other genetic group (30.2%) reached the composite outcome of all-cause mortality/Htx (p=0.022) (figure 2). However, adjusting for the presence of RVD at follow-up abolished the observed difference (p=0.245) (figure 2; Supplementary table S5).

Sensitivity analyses

Considering only the probands in cases of familial clusters, 94 patients were identified (46 affected by *TTN* related DCM (49%) and 48 (51%) with other genetic etiology; see Supplementary table S1).

The baseline characteristics of this cohort are reported in Supplementary table S6. The results in this cohort were consistent with the main analysis. In particular, *TTN* related DCM was associated with significant improvement of RV function during follow-up, while persistent RVD was observed in the other genetic DCM group (Supplementary table S6 and Supplementary figure S3).

Genetically tested negative DCM cohort

A cohort of 139 genetically tested negative DCM patients with available follow-up data and adequate echocardiographic windows to calculate RVFAC were included as a control group. Compared to the genetically determined DCM cohort, genetically tested negative patients were older, more likely to suffer from associated hypertension, and had a higher prevalence of LBBB and LA dilatation. All the other clinical and echocardiographic characteristics were similar between the two groups (Supplementary table S7). In particular, there were no significant difference in RVFAC (41±12 vs 39±11%, respectively, in genetically negative vs genetically positive patients; p=0.304) and the prevalence of RVD was also comparable (28.6% vs 28.8%; p= 1.000).

At follow-up, genetically tested negative patients significantly improved their RVFAC (from 41±12% to 44±8%; p<0.001) and the prevalence of RVD dropped from 28.8% to 7.8%.

Interestingly, at follow-up evaluation, both RVFAC and the prevalence of RVD were similar between genetically negative patients and those affected by *TTN* related DCM (44±8% vs 46±7%; p=0.157 and 7.8% vs 5.9%; p=0.764, respectively). Conversely, when compared with other genetic etiologies, genetically negative patients had a significantly higher RVFAC (44±8% vs 36±10%; p<0.001) and showed a lower prevalence of RVD (7.8% vs 35.8%; p<0.001) (table 4).

The unadjusted outcome measure was similar in genetically negative patients compared to those with pathogenic *TTN* mutations (p=0.390), while it was significantly better than the one of patients affected by other genetic etiologies (p=0.047) (Supplementary figure S4).

Discussion

This analysis aimed to investigate the complex interplay between ventricles in DCM in one of the largest reported series of patients with available genetic testing and follow-up data. We report 3 important findings. First, the prevalence of RVD at clinical presentation is comparable in different genetic DCM subgroups. Second, most patients with *TTN* related DCM and genetically negative DCM improve their RV function with GMT and very rarely develop *de novo* RVD after their index presentation. In contrast, other genetic etiologies are less frequently associated with normalization of RV function and, in a non-negligible number of cases, show a late RV involvement during the natural progression of the disease. Finally the presence of RVD at initial presentation and a genetic background other than *TTN* are independently associated with the persistence RVD at follow-up.

RV dysfunction in DCM

DCM represents the second most common HF etiology with a higher prevalence of RV involvement compared to ischemic heart disease [9]. However, few large-scale studies have previously described the prevalence and prognostic role of RV dysfunction in patients with DCM. Gulati et. al demonstrated, in a cohort of DCM patients investigated with cardiac magnetic resonance (CMR), that up to one third might present with RVD at the first clinical presentation [8]. Furthermore, after adjustment for other established prognostic factors, patients with baseline RVD had a 4-fold increase in cardiovascular mortality or HTx [8]. Nevertheless, our group formerly documented that RVD is a dynamic process in the natural history of DCM and, while most patients normalize their RV function following GMT, persistent or late-onset RVD are strongly associated with poor prognosis [10].

In the present analysis, we develop this understanding by describing, for the first time, difference according to genetic background. Approximately one third of cases presented with RVD, regardless of genetic background. However, we describe a different evolution in *TTN* related DCM patients compared to other genetic pathogenic variants. In fact, most patients in the *TTN* related DCM significantly improved their RV function over time, and only approximately 5% of patients still had RVD after a median of 14 months since diagnosis. On the contrary, patients with other genetic etiologies and RVD at first clinical presentation mostly maintained it during follow-up, and, in a non-negligible number of cases (17.6%; table 2), a subsequent worsening of RV function in the successive two years after the initial presentation was documented. This was supported by the multivariable model, where a genetic background other than *TTN* was strongly and independently associated with the presence of RVD at follow up (p=0.001).

This finding is intriguing, and suggests that *TTN* related DCM is rarely a biventricular disease. Indeed, RVD at the first clinical presentation will normalize it in the subsequent clinical course, being likely representing hemodynamic impairment rather than structural disease or being more amenable to treatment. Therefore, appreciating the genetic background in patients presenting with DCM may be important to predict the dynamic evolution and the possible persistence of RVD, [20], which is associated with a poorer global outcome (figure 2).

TTN related DCM and cardiac reverse remodeling: a benign mutation?

TTN pathogenic mutations are the most frequent cause of genetically determined DCM, representing almost 1/3 of this cohort [4]. *TTN* related DCM is thought to be associated with a milder phenotype of the disease and a particularly high rate of LVRR with GMT [5-7].

Previous studies have reported that genetically determined DCM patients are less prone to favorable LVRR compared to their genetically negative counterparts [5]. Interestingly, this

difference was not evident in patients with *TTN* mutations compared to genetically negative patients [5].

In our analysis, we confirmed that *TTN* related DCM has a higher incidence of LVRR compared to other genetic etiologies (p=0.049). Furthermore, we also demonstrated that RVD recovery is also similar in *TTN* related DCM and genetically negative DCM, reaching approximately 80% in both groups. The latter finding is totally new and assumes that pathogenic *TTN* mutations might lead to a milder form of genetically determined DCM, in whom there is a higher likelihood of global cardiac reverse remodeling with GMT.

Outcomes in genetically determined DCM; a matter of RVD?

After adjusting for the presence or absence of RVD at follow-up, no differences in the composite endpoint of all-cause mortality and HTx were evident (figure 2).

This reinforces the importance of genotyping DCM patients. Indeed, in presence of *TTN* related DCM, RVD might represent a therapeutic target. Conversely, in other genetic etiologies, RVD is more likely the epiphenomenon of advanced disease.

These results are promising, but the low number of events in our population did not allow us to adjust the differences in clinical outcomes for other variables, representing an important limitation. Furthermore, a trend toward a worse outcome for patients with other genetic DCM was seen. Future studies should be designed in order to assess this important concept.

Study limitations

This study has the intrinsic limitation of all observational, registry studies. As patients are enrolled from a referral center for cardiomyopathies, the results might not be generalizable for all DCM patients.

The enrolment period was long, starting in 1995, and several important advances in GMT guideline-directed medical treatment occurred in this time.

Brain natriuretic peptides levels were not systematically available and could not be included in the preset analysis. Drug doses were also not available but, importantly, we did not observe any baseline and follow-up differences in rates of prescription.

The multivariable included only 3 variables due to the low number of events, which limited the statistical power of our analysis. However, we performed two sensitivity models where both RVD and the genetic background remained significant.

Tricuspid annular plane excursion (TAPSE) was available only in a minority of patients, and RVD was only defined using RVFAC.

Two-dimensional echocardiography clearly manifests some limitations in the assessment of RV compared to CMR. However, we performed an inter-observer and intra-observer variability analysis that indicated a good performance level (ICC 0.929; 95% CI 0.888-0.958; $p<0.001$; kappa agreement 0.84 and 0.81 for intra-observer and inter-observer analysis respectively) and we previously reported good correlation between echocardiographic RVFAC and CMR RV ejection fraction in a series of 50 DCM patients [10].

Unfortunately, the low number of patients for each single pathogenic mutation did not allow us to draw any conclusions regarding the possible prevalence of RV involvement in single specific mutations, and this should be pursued in the future.

Conclusions

RVD is present in almost one third of DCM. However, while the majority of patients affected by *TTN* related DCM and patients without a demonstrable pathogenic variant normalize their RVD during follow-up, other genetic backgrounds mostly maintain it, which is associated with worse outcome. These results suggest that the evolution of RVD is heterogeneous in genetically determined DCM and genotyping appears pivotal in this context. These finding should be confirmed in larger series.

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Table 1: Baseline characteristics of the study population.

Characteristics	Genetically positive cohort (n=104)	*TTN* related DCM (n=51; 49%)	Other genetic DCM (n=53; 51%)	P value
Age (years) (0)	42±15	47±14	37±15	**0.002**
Male sex (%) (0)	78 (75%)	40 (78%)	38 (71%)	0.500
Time since HF diagnosis (months) (6)	1 (0-8)	1 (0-8)	1 (0-7)	0.82
Hypertension (%) (0)	22 (21.2%)	12 (23.5%)	10 (18.8%)	0.635
SBP (mmHg) (10)	119±16	119±18	120 ± 16	0.712
NYHA III-IV (%) (0)	13 (12.5%)	6 (11.8%)	7 (13.2%)	1.000

Beta-blockers (%) (0)	86 (82.7%)	46 (95.8%)	40 (83.3%)	0.091
ACEI/ARBs/ARNI (%) (0)	95 (89.4%)	47 (92.2%)	46 (86.8%)	0.527
Loop diuretics (%) (0)	52 (50%)	23 (45.3%)	29 (54.7 %)	0.220
CRT (during follow up) (%) (0)	10 (9.6%)	5 (9.8%)	5 (9.4%)	1.000
ICD (during follow up) (%) (0)	44 (42.3%)	25 (49%)	19 (35.8%)	0.234
HR (bpm) (12)	76±17	78±19	73±18	0.053
QRS length (ms) (31)	102±24	103±19	101±28	0.734
LBBB (%) (0)	10 (9.6%)	6 (11.7%)	4 (7.5%)	0.740
Echocardiography				
LVEF (%) (2)	33±10	33±11	34±10	0.400
iLVEDD (mm/m2) (5)	34±6	34±6	35±5	0.059
iLVEDV (ml/m2) (6)	94±32	93±33	94±34	0.295
LAESA (cm2) (12)	25±8	26±8	24±8	0.240
RVFAC (%) (0)	39±11	42±11	35±11	**0.011**
RVD (%) (0)	30 (28.8%)	11 (21.6%)	19 (35.8%)	0.132
Moderate-severe MR (%) (0)	34 (32.7%)	19 (37.3%)	15 (28.3%)	0.404

P values are referred to the comparison between *TTN* related DCM and other genetic DCM and reported in bold when significant (i.e.<0.05). In the first column, the number in parentheses represents the overall number of genetically tested positive patients with missing data.

DCM= dilated cardiomyopathy; SBP= systolic blood pressure; NYHA =New York Heart Association; ACEI: angiotensin-converting enzyme inhibitors; ARB= angiotensin receptor blockers; ARNI= angiotensin receptor neprilysin inhibitor; CRT= cardiac resynchronization therapy; ICD= implantable cardiac defibrillator; HR= heart rate; LBBB= left bundle branch block; LVEF= left ventricular ejection fraction; iLVEDD= indexed left ventricular end-diastolic diameter; iLVEDV= indexed left ventricular end-diastolic volume; LAESA= left atrial

end-systolic area; RVFAC= right ventricular fractional area change; RVD= right ventricular dysfunction; MR= mitral regurgitation.

Table 2: Evolution of right ventricular dysfunction and rates of left ventricular reverse remodelling of the study population at follow-up.

Characteristics	*TTN* related DCM (n=51; 49%)	Other genetic DCM (n=53; 51%)	P value
LVRR (%)	19/51 (37.2%)	10/53 (18.8%)	**0.049**
RVFAC (%) (0)	46±7	36±10	**<0.001**
RVD (%) (0)	3 (5.9%)	19 (35.8%)	**<0.001**
Persistent RVD (%) (0)	2/11 (18.1%)	13/19 (68.4%)	**0.004**
Incident RVD (%) (0)	1/40 (2.5%)	6/34 (17.6%)	0.09

Significant p values are reported in bold. In the first column, the number in parentheses represents the overall number of genetically tested positive patients with missing data

RVD= right ventricular dysfunction; LVRR= left ventricular reverse remodelling. **Persistent RVD=** patients who presented RVD both at baseline and follow up; **Incident RVD=** patients with a normal RV function at baseline who developed RVD subsequently at follow-up. See supplementary table S2 for complete characteristics at follow-up of the study population.

Table 3: Multivariable analysis for persistence or incidence of RV dysfunction at follow-up.

	OR	95% CI	P value
Other genetic DCM vs *TTN* related DCM	16.458	3.095-87.513	**0.001**
LVEF (%)	0.962	0.902-1.025	0.231
RV dysfunction at baseline (%)	6.776	1.976-23.239	**0.002**

Significant p values (i.e<0.1) are reported in bold. DCM= dilated cardiomyopathy; LVEF= left ventricular ejection fraction; RV= right ventricular. The univariable analysis is reported in supplementary table S3.

Table 4: Prevalence of RV dysfunction in genetically positive and genetically negative DCM at follow-up.

	Genetically negative DCM (n=139)	*TTN* related DCM (n=51)	Other genetic DCM (n=53)	P value
RVFAC (%)	44±8	46±7	36±10	**<0.001 *£**
RVD (%)	11 (7.8%)	3 (5.9%)	19 (35.8%)	**<0.001*£**
Persistent RVD	7/40 (17.5%)	2/11 (18.1%)	13/19 (68.4%)	**0.004 £; <0.001***
Incident RVD at follow-up	4/99 (4.1%)	1/40 (2.5%)	6/34 (17.6%)	**0.01 ***

Only significant p values (i.e. < 0.05) are reported. *=genetically negative DCM vs other genetic DCM; £= *TTN* related DCM vs other genetic DCM. DCM= dilated cardiomyopathy; RVFAC= right ventricular fractional area change; RVD= right ventricular dysfunction;

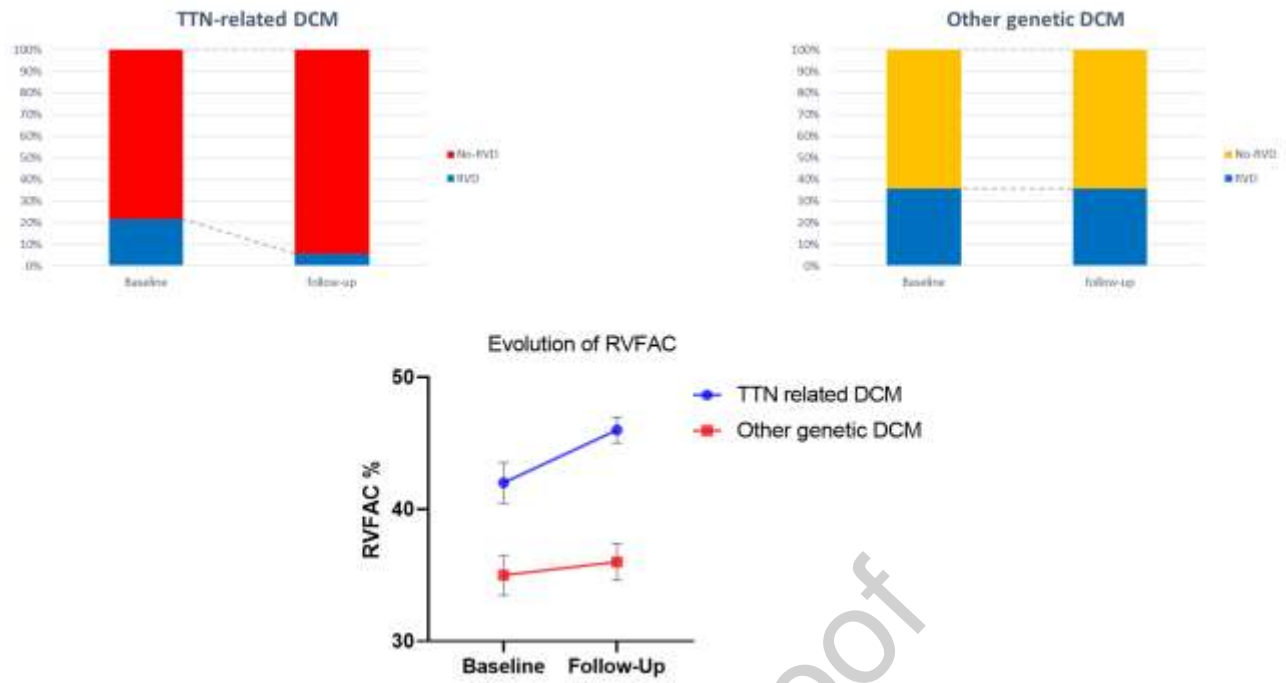

Fig 1. Evolution of RVFAC and prevalence of RV dysfunction at baseline and follow-up in the two genetic cohorts.

RVFAC= Right ventricular fractional area change; DCM= Dilated Cardiomyopathy. In blue patients affected by *TTN* related DCM, in red patients affected by other genetic DCM. Data are mean and Standard Error of the mean.

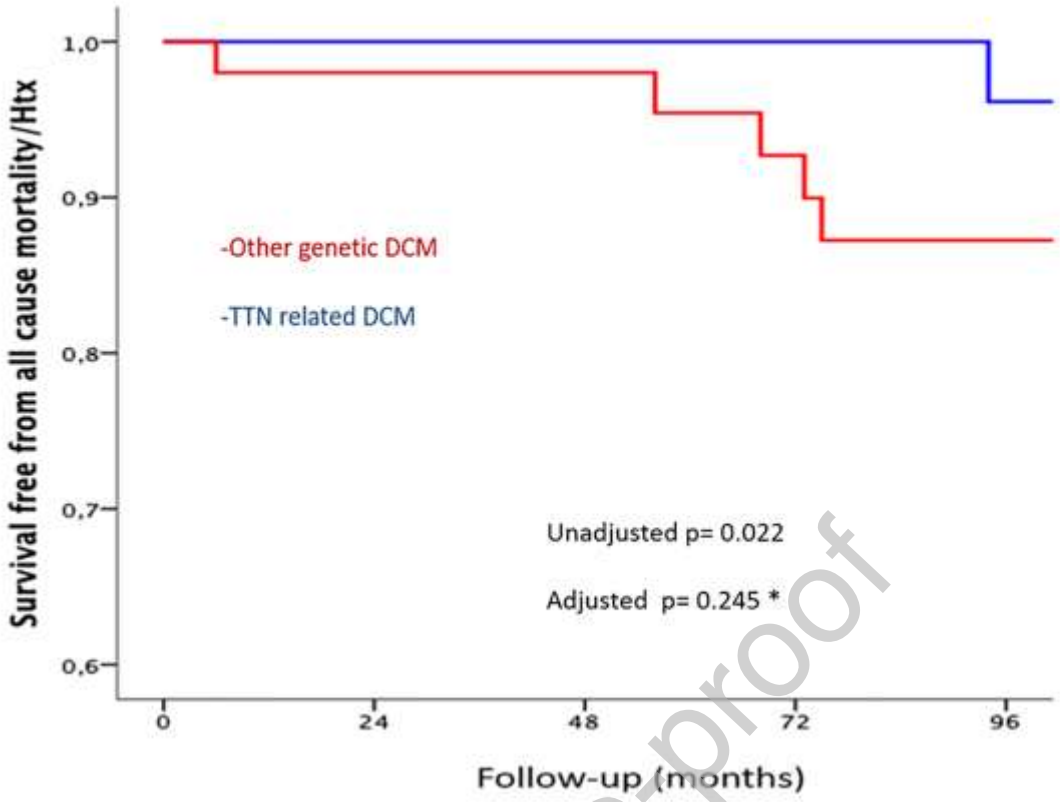

Fig. 2 KM survival curves for all-cause mortality/Htx. The baseline was intended as the 14 [10-18] month evaluation.

Htx= heart transplantation; DCM= dilated cardiomyopathy. In blue TTN-related DCM, in red other genetic DCM. * p value adjusted for right ventricular dysfunction at follow-up.