Internal and Emergency Medicine (2019) 14:1299–1306
https://doi.org/10.1007/s11739-019-02114-3

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Prevalence and prognostic impact of left ventricular non-compaction in patients with thalassemia

Rodolfo Bonamini[1] · Massimo Imazio[2] · Riccardo Faletti[1] · Marco Gatti[1] · Borejda Xhyheri[3] · Marco Limone[4,5] · Filomena Longo[4,5] · Antonio Piga[4,5]

Received: 29 November 2018 / Accepted: 23 May 2019 / Published online: 25 June 2019

Abstract
A high incidence of isolated left ventricular non-compaction (LVNC) has been reported in previous studies on smaller cohorts of patients with thalassemia by cardiac MRI but the clinical impact of the finding is unknown. This prospective cohort study evaluates the prevalence and clinical implication of the finding. Prospective cohort study with enrollment of all consecutive cases with thalassemia referred for cardiac MRI from September 2007 to November 2014. The presence of LVNC was assessed according to the Petersen method and the Jacquier method, with the proposed changes by Fazio, Grothoff, and Chiodi. A clinical follow-up was performed in all patients. We included 560 patients with thalassemia (473 with thalassemia major and 87 with thalassemia intermedia: mean age 31.9 ± 10.6 years, male/female = 250/310). A total number of 1683 MRI tests were performed. A diagnosis of LVNC was determined according to adopted MR criteria in 44 patients (7.9%). Patients with LVNC had a significantly lower ejection fraction (52.68 ± 5.17% vs. 56.90 ± 6.34%; $p = 0.0005$) and greater indexed LV ESV (48.16 ± 10.03 ml/m^2 vs. 40.02 ± 10.06 ml/m^2; $p = 0.0022$). After a mean follow-up time was 5.1 years, no significant change of MR parameters was detected as well as no clinical adverse events. LVNC is relatively frequent in patients with thalassemia. However, it is not associated with a worsening of LV function and adverse events after a long-term follow-up.

Keywords Thalassemia · Left ventricular non-compaction · Cardiac magnetic resonance · Prognosis

Introduction

The ability of magnetic resonance imaging (MRI) to detect and monitor the otherwise silent iron infiltration of cardiac tissue has truly revolutionized the management of iron overload disorders [1]. On this basis, the use of MRI to quantitate organ iron burden has become the routine technique in clinical practice either for the clinical management or the periodic control of thalassemia patients [1–6].

Left ventricular non-compaction (LVNC) is a rare congenital disorder that is commonly attributed to intrauterine arrest of normal compaction during the myocardial morphogenesis [7–9]. Although initially described as a relatively rare entity, its prevalence has been increasingly reported in several conditions either isolated or not, especially as incidental finding during imaging studies [10–18]. Hypertrabeculation has been linked to a number of congenital cardiac and sometimes non-cardiac disorders. Nonetheless, cases have also been reported in adults with no obvious congenital disease, and the term isolated LVNC was used to describe such cases. Few reports described cases of isolated LVNC in hematological disorders [19–23].

The purpose of this work is to verify the incidence of LVNC using more up-to-date and more specific LVNC MRI diagnostic methods and evaluate the clinical and instrumental evolution of these patients in a long-term follow-up.

✉ Massimo Imazio
massimo_imazio@yahoo.it

1 Department of Surgical Sciences, Radiology Unit, University of Torino, Turin, Italy

2 University Cardiology, AOU Città Della Salute e Della Scienza Di Torino, Corso Bramante 88, 10126 Turin, Italy

3 Nuovo Ospedale Degli Infermi, Ponderano, Biella, Italy

4 Department of Clinical and Biological Sciences, University of Torino, Turin, Italy

5 Reference Centre for Hemoglobinopathies, AOU San Luigi Gonzaga Hospital, Orbassano, Italy

Methods

Study design and patient population

The study is an observational study including all consecutive patients with beta-thalassemia presenting to our center for cardiac iron assessment by cardiac MR. The study conforms to the Helsinki Declaration and was performed at the Department of Clinical and Biological Sciences, University of Torino, Reference Centre for Hemoglobinopathies, AOU San Luigi Gonzaga Hospital, Orbassano, Italy. This is a reference center for the control and the follow-up of thalassemia patients in the Piedmont region as well as for other Italian regions.

The monitoring procedure consisted of an accurate and thorough clinical and laboratory examination, including also ECG and MRI of the heart and the liver. The concentration of iron in the liver was measured also with Biomagnetic Liver Susceptometer SQUID (superconducting quantum interference device).

This study consists of a supplement of analysis performed on magnetic resonance images obtained as part of the regular control program in a population of patients with thalassemia.

Between September 2007 and November 2014, 560 patients with thalassemia (473 with thalassemia major and 87 with thalassemia intermedia), regularly followed in the Centre, performed MRI examination to monitor iron burden and heart function; repeated checks were required in many patients; thus 1683 MRI controls were performed in these patients. All patients in whom a MRI was performed were in sinus rhythm and signed a written informed consent.

Patients' records were reviewed using paper-based clinical records and Webthal [24], a computerized clinical record for thalassemia developed internally. Data collected include demographic data as date of birth, gender and age and clinical data as diagnosis, the history and familiarity of heart disease, hypothyroidism, hypoparathyroidism, splenectomy status, positivity for anti-HCV antibody and qualitative HCV RNA test, history of thrombosis and iron chelation therapy.

All patients subjected to cardiac MRI evaluation had laboratory measurements for total hemoglobin (Hb), serum ferritin (automated immunofluorescence assay; BRAHAMS Ferritin KRYPTOR), alanine aminotransferase, serum iron and transferrin levels and body surface area.

MRI study

All cardiac MRI studies were performed on Philips Achieva 1.5-Tesla MR systems (Philips Healthcare, Best, The Netherlands), equipped with a five-element SENSE cardiac coil using the same scanning protocol. All sequences were ECG gated. All images were acquired in end-expiratory breath-old. After the acquisition of scout images, fast imaging with steady-state-free precession loops were acquired in four-chamber, two-chamber, three-chamber views and parallel slices in short-axis planes with zero interslice gap to cover the entire ventricles (retrospective gating; slice thickness = 8 mm; gap = 0; echo time [TE] = 1.67 ms; repetition time [TR] = 3.3 ms; flip angle = 60°). A Philips IntelliVue EWS system was used for quantitative analysis of CMR images to evaluate heart dimensions and function, manually contouring end-diastolic and end-systolic myocardium, compacted and non-compacted. Patients were also evaluated for cardiac and liver siderosis measuring T2* time. Myocardial T2* was calculated using single short-axis, mid-ventricular slices ECG triggered, breath-hold acquired at eight TEs (2, 3, 4, 6, 9, 12, 15, and 18 ms). A gradient-echo sequence was used (flip angle = 20; pixel dimension = 2.1 mm; repetition time = 21 ms). Images at different TEs were coregistered to correct for variations in end-expiratory cardiac position. Signal decay curves were measured using a full-thickness region of interest in the interventricular septum.

Liver T2* was calculated using single axial slices at middle liver level in breath-hold without ECG trigger, acquired at nine TEs (1, 1.25, 1.5, 2, 3, 4, 6, 9 and 18 ms). A gradient-echo sequence was used (flip angle = 20; pixel dimension = 2.1 mm; repetition time = 21 ms).

Signal decay curves were measured using a large, full-thickness region of interest in the liver, excluding vascular tree.

Both in heart and liver images, the trend line was fitted to a monoexponential decay model, with an equation of the following form:

$$S = S_0 e^{(\mathrm{TE}/\mathrm{T2}*)},$$

where S represents the fitted signal, S_0 represents the initial amplitude, and T2* represents the relaxation constant.

Liver iron concentration (LIC) was also measured using Biomagnetic Liver Susceptometer (Biosusceptometer SQUID 5700, TRISTAN TECHNOLOGIES Inc, San Diego, CA, USA) [25]. Liver stiffness was evaluated by transient elastography (FibroScan1; Echosens, Paris, France) [26].

The search for the presence of LVNC was performed as follows: all the cine images of the first CMR performed, both in long axis projections and in all short-axis projections, were visually analyzed to verify the presence of distinct two-layered appearance of trabeculated and compacted myocardium. When research has given positive results, two methods of analysis have been applied: the Petersen method [27] and the Jacquier method [28], with the proposed changes by

Fazio [29] and Grothoff [30], considering also the suggestions of Chiodi [23].

All cases with the following three criteria were considered positive:

- Diastolic $M_{\text{non-compacted}}/M_{\text{total}}$ percentage > 25%
- Diastolic $M_{\text{non-compacted}}$/BSA > 15 g/m^2
- Diastolic non-compacted/compacted myocardium ratio of > 2.5 in at least one of the segments excluding the apical segment 17.

Visual analysis and all measurements in positive cases were made by an experienced observer in cardiac imaging (R.B. 20 years of experience in CMR).

To evaluate interobserver variability, some parameters (End-Diastolic Volume-EDV, FE, ED-NC%) were measured in double blind by a second operator (M.G. 4 years of experience in CMR) in all patients with LVNC and follow-up.

In none of the patients with LVNC, a neuromuscular disorder or congenital heart disease was detected. We performed MRI examination also in two families of patients with LVNC and all first-degree relatives were normal.

Statistical analysis

Continuous variables are given as mean ± standard deviation and compared by the Student's *t* test. Categorical variables are expressed as number and percentage and compared by Chi-square test, and the level of significance $p < 0.05$ was considered statistically significant.

The paired data were represented by linear plot correlated with Pearson's linear correlation coefficient.

To compare two related samples as base-follow-up values and interobserver variability, the non-parametric Wilcoxon's signed-rank test was used together with intercorrelation coefficient (ICC) measures derived from variance within and variance between the two samples (ANOVA) and the Bland–Altman plot to evaluate the agreement among paired measurements. SPSS Statistical Software version 20.0 was used for statistical analysis.

Results

Baseline data

The studied population included 560 patients with thalassemia (mean age 31.9 ± 10.6 years, male/female = 250/310). Baseline characteristics of the studied population are reported in Table 1. According to the established MRI criteria for the diagnosis of LVNC, a diagnosis of LVNC was determined in 44 patients (7.9%). An example of a patient with LVNC detected on MRI is depicted in Fig. 1. Table 2 displays main cardiac MRI parameters and characteristics of patients with LVNC.

Table 1 Patients' characteristics. Comparison of thalassemia patients' characteristics between group without LVNC and with LVNC (total no of β-Thalassemia patients = 560)

	No LVNC	LVNC	*p* value	TOT ± SD
Patients no (% of total)	516 (92.1)	44 (7,9)		560
Age (years)	31.8 ± 10.7	32.2 ± 8.9	0.4121	31.9 ± 10.6
Sex (m/f)	228/288	22/22	0.5598	250/310
BSA (m^2)	1.61 ± 0.16	1.58 ± 0.16	0.3809	1.6 ± 0.2
EDV/BSA (ml/m^2)	92.56 ± 17.81	101.43 ± 16.82	0.0748	
ESV/BSA (ml/m^2)	40.02 ± 10.06	48.16 ± 10.03	0.0022	
EF (%)	56.90 ± 6.34	52.68 ± 5.17	0.0005	
Splenectomized, *n* (%)	253 (49)	21 (47.7)	0.926	277 (49.4%)
Iron chelation therapy (224), *n* (%)	202 (39)	22 (50)		224 (40%)
Deferoxamine	59	9		68
Deferiprone	58	3		61
Deferoxamine/Deferiprone combination	39	5		44
Deferasirox	46	5		51
Mean total hemoglobin ± SD, g/dL	9.7 ± 0.5	9.8 ± 0.5	0.126	9.7 ± 0.5
Mean serum ferritin ± SD, ng/mL	1619.8 ± 1705.8	1162.1 ± 1191.4	0.071	1580 ± 1671.3
Mean heart T2* ± SD, msec	36.2 ± 13.9	33.8 ± 12.6	0.297	36 ± 13.8
Mean LIC ± SD, microg Fe/g wet weight	1417.6 ± 954.4	1562.0 ± 1254.7	0.393	1429.9 ± 982.6
Mean ALT ± SD, IU/L	59.2 ± 39.1	51.2 ± 40.8	0.777	49.3 ± 39.2
Mean liver stiffness ± SD, kPa	7.2 ± 5.9	6.0 ± 2.0	0.243	7.1 ± 5.7

BSA body surface area, *EDV* end-diastolic volume, *ESV* end-systolic volume, *EF* ejection fraction, *LIC* liver iron concentration

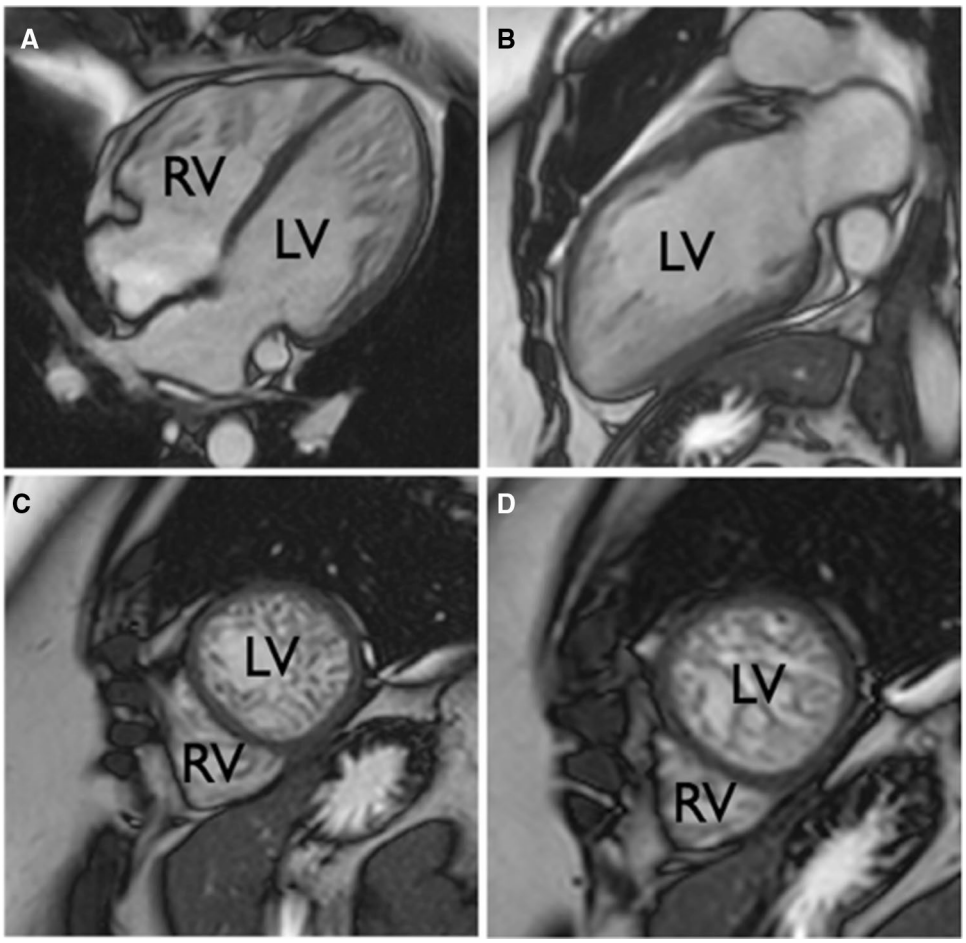

Fig. 1 A case of a patient with thalassemia and LVNC according to CMR criteria defined in the methods. **a** Four-chamber view, **b** two-chamber view, **c**, **d** short-axis views of the ventricles. *LV* left ventricle, *RV* right ventricle

Patients with LVNC had a significantly lower ejection fraction ($52.68 \pm 5.17\%$ vs. $56.90 \pm 6.34\%$; $p = 0.0005$) and greater indexed LV End-Systolic Volume -ESV (48.16 ± 10.03 ml/m^2 vs. 40.02 ± 10.06 ml/m^2; $p = 0.0022$) (Table 1). There were no significant differences related to the frequency of splenectomized patients, iron chelation therapy, or hematological parameters between the two groups (Table 1). None of the 560 patients with thalassemia showed CMR signs of thrombi in the heart chambers using the sequences illustrated in the previous section.

Follow-up data

The average follow-up time was 5.1 years (min: 2.0, max: 6.9, SD: 1.3). During follow-up, no adverse events occurred in patients with thalassemia and LVNC. CMR parameters did not show LV dilatation and significant changes of the LV ejection fraction (Table 3). Moreover, the amount of the LVNC mass was unchanged (Table 3) (Fig. 2).

Comparison of base-follow-up CMR data with matched distributions and interobserver variability analysis are reported in Tables 3 and 4. Interobserver variability analysis showed a very good correlation between two observers (Table 4).

Discussion

American Heart Association (AHA) has classified LVNC as a primary genetic cardiomyopathy [31], whereas the European Society of Cardiology (ESC) reported LVNC as an unclassified cardiomyopathy [32]. Rather than being an all-or-none phenomenon, the extent of myocardial compaction may show a spectrum of disease within the population, with only a subgroup of patients with LVNC as a real disease, and others where LVNC can be considered a benign variant and not a cardiomyopathy [33]. The diagnosis can be made especially with two-dimensional echocardiography, and cardiac magnetic resonance imaging. The prevalence and incidence of LVNC varies between case studies and is still not well defined. The reported prevalence in patients referred to echocardiography laboratories ranges between 0.014 and 1.3% [34, 35], depending on the age at the first diagnosis [36] and the diagnostic technique used. At present, unique and reproducible diagnostic criteria are still lacking and differences

Table 2 Main CMR parameters in all patients with LVNC

PT no	EDV ml	ESV ml	EF%	NC M/BSA	NC mass%	NC/C	EDV/BSA ml/m^2	ECG	Heart disease
1	136.34	62.11	54	29.58	39	3.86	100.98	N	N
2	217.54	96.81	55	33.14	32	4.66	124.88	N	N
3	166.54	80.71	52	23.73	31	3.22	105.11	N	N
4	193.81	83.06	57	29.83	33	3.58	119.58	N	N
5	129.50	60.35	53	24.23	35	3.40	80.77	N	DCM
6	114.59	56.14	51	20.76	29	2.94	70.97	N	N
7	153.04	59.22	61	26.11	30	3.28	93.78	N	N
8	102.63	35.82	65	19.22	33	3.35	68.81	N	N
9	181.06	94.82	48	30.80	35	3.93	107.59	N	N
10	193.78	88.12	58	39.36	36	3.47	126.80	N	N
11	176.78	104.20	41	36.42	37	3.70	122.62	T- (II, III, aVF, V3-6)	N
12	115.98	58.33	50	22.64	36	3.44	89.89	N	HF
13	135.05	63.37	53	25.89	36	3.66	88.56	N	N
14	162.98	77.77	52	22.36	27	3.13	89.47	N	N
15	118.40	57.30	52	19.90	31	3.18	79.37	N	N
16	159.00	64.14	60	30.51	38	2.92	98.64	N	N
17	104.60	55.73	47	24.65	36	3.59	80.28	LAFB T- (II, III, V2-6)	N
18	215.88	97.17	55	33.05	35	3.89	128.96	N	SCMP
19	183.11	87.84	52	31.88	33	3.46	118.06	N	N
20	198.30	87.03	56	28.73	35	3.70	105.13	RBBB I	N
21	226.92	98.08	57	30.20	32	3.36	118.87	N	N
22	234.39	103.04	56	36.60	36	3.01	127.72	N	N
23	164.14	98.97	40	31.21	36	3.08	100.48	N	N
24	236.20	117.62	50	30.22	31	3.33	116.93	N	PH
25	136.56	66.29	51	21.33	34	2.76	83.66	N	N
26	149.78	66.59	56	17.77	27	3.21	93.68	N	N
27	180.02	93.02	48	33.03	36	4.00	123.43	S1S2S3	N
28	125.51	68.62	45	39.74	49	3.56	89.50	N	DCM + PAF
29	160.13	65.69	59	26.68	30	3.08	108.15	N	N
30	190.11	106.43	44	28.16	29	3.18	117.39	N	N
31	135.07	60.72	55	20.00	29	3.27	95.84	LAFB T- (II, III, V3-6)	N
32	117.98	62.57	47	23.42	29	3.41	94.76	N	PH + PAF
33	149.33	62.10	58	18.94	30	4.28	90.60	N	SH
34	98.78	47.74	52	21.86	36	2.73	72.82	N	N
35	154.11	77.92	49	33.76	36	2.55	101.07	N	N
36	145.44	59.82	59	26.18	36	4.18	91.63	N	N
37	165.50	75.53	54	32.07	33	4.15	110.10	N	N
38	185.02	90.34	51	42.79	40	3.78	115.11	N	N
39	181.83	70.50	61	27.92	34	3.26	104.19	N	N
40	234.98	122.97	48	35.93	33	2.82	134.00	N	N
41	131.35	63.47	52	32.41	33	3.20	80.20	N	DCM
42	148.66	70.73	52	41.69	42	2.74	94.53	1 APC	N
43	151.12	73.98	51	23.48	31	2.71	102.89	N	N
44	146.41	72.20	51	27.64	36	3.46	95.15	N	HF

EDV end-diastolic volume, *ESV* end-systolic volume, *EF* ejection fraction, *NC* non-compacted *C* Compacted, *BSA* body surface area, *DCM* dilated cardiomyopathy, *HF* heart failure, *PAF* paroxysmal atrial fibrillation, *PH* pulmonary hypertension, *SCMP* siderotic cardiomyopathy, *SH* systemic hypertension

Table 3 Comparison of baseline-follow-up CMR data with matched distributions

	EDV baseline-FU	EF baseline-FU	Mass NC baseline-FU	NC/C ratio baseline-FU	Mass NC% baseline-FU	NC/BSA baseline-FU
LVNC patients comparison baseline-FU						
Pearson product moment correlation coefficient	0.87	0.62	0.82	0.78	0.79	0.74
Wilcoxon *p*	0.88	0.15	0.77	0.11	0.79	0.48
ICC intercorrelation coefficient	0.86	0.56	0.80	0.78	0.89	0.85
Bland–Altman plot mean difference ± SD	4.2 ± 18.9	– 2.1 ± 4.6	0.8 ± 7.0	0.04 ± 0.3	– 0.4 ± 2.6	0.6 ± 4.4
Limits of agreement	41.3, – 32.9	6.9, – 11.1	14.4, – 12–8	0.58, – 0.49	4.7, – 5.5	9.2, – 8.0

EDV end-diastolic volume, *EF* = ejection fraction, *NC* = non-compacted, *C* compacted

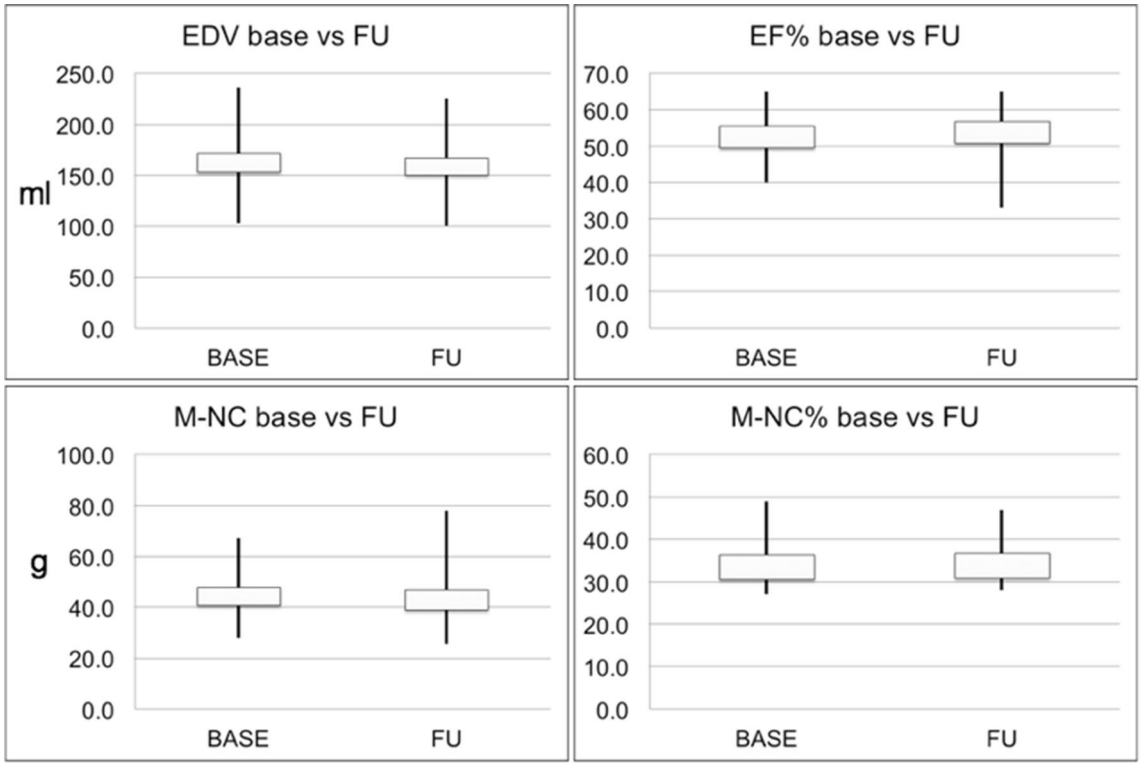

Fig. 2 Left ventricle EDVs, ejection fraction (EF), and LVNC mass in absolute values and percentages by CMR at baseline and follow-up. No significant change was detected in all these parameters of patients with thalassemia and LVNC

in the prevalence of various studies may be due to different in diagnostic criteria, and imaging techniques. Even the prognosis has a wide variability that depends mainly on the presence of LV dysfunction, the presence of late gadolinium enhancement [36], and on the cardiac condition at the time of the first diagnosis. Patients with reduced cardiac function always have a worse prognosis [37], but it is not clear whether it depends on the cardiac condition or the presence of LVNC.

As previously specified, we have used in all cases cardiac MR as a diagnostic technique, adopting the most stringent diagnostic criteria of the literature.

At present, this is the largest study evaluating the prevalence of LVNC in patients with thalassemia. In patients with beta-thalassemia, the prevalence of LVNC is relatively high (about 8% in this study) even when assessed by strict MR criteria, as delineated in the methods. However, this incidental finding by imaging is not associated with LV progressive

Table 4 Interobserver variability analysis

	EDV	EF	Mass NC%
Interobserver variability			
Pearson product moment correlation coefficient	0.99	0.82	0.81
Wilcoxon *p*	0.67	0.23	0.75
ICC intercorrelation coefficient	0.99	0.84	0.75
Bland–Altman plot Mean difference ± SD	4.2 ± 18.9	– 2.1 ± 4.6	0.8 ± 7.0
Limits of agreement	41.3, – 32.9	6.9, – 11.1	14.4, – 12.8

dilatation or worsening of LV function as well as clinical events.

In our previous study, a prevalence of 13% was detected in 135 patients with beta-thalassemia [21], but without a specific evaluation of the clinical implication of the finding.

In previous reports from the non-thalassemic population, isolated LVNC was associated with significant morbidity, including end-stage heart failure, cerebrovascular events due to cardiac emboli, and ventricular arrhythmias; however, the incidence of these outcomes varies widely between different studies [38].

The rates of mortality and heart transplantation have ranged from as high as 40% [17] to as low as 3% [18]. Additionally, the use of different diagnostic criteria to identify LVNC further illustrates the interpretation of outcomes [39–42].

In patients with beta-thalassemia, where cardiac diseases remain a primary cause of mortality, LVNC can have also negative prognostic implications that are worthy of investigation [22].

In the present study on a larger population of patients, we have confirmed the high prevalence of LVNC. The explanation of the finding remains unknown. In our previous study, we have speculated that ineffective erythropoiesis and chronic anemia/hemolysis may lead to chronic oxidative and inflammatory stress triggering myocardial remodeling and transformation from compact musculature to the spongy myocardium, thus leading to an acquired form of LVNC [21].

In any case, a long-term follow-up based on clinical evaluation and repeated cardiac MR studies shows that cardiac MR parameters are unchanged with no progressive LV dilatation or dysfunction. At the same time, we have documented no cardiac mortality and clinical events in these patients suggesting that LVNC seems to have no negative prognostic implications.

In conclusion, the finding of LVNC in patients with beta-thalassemia is relatively common (about 8%) but not associated with worsening of LV function and clinical events after a long-term follow.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

Statement of human and animal rights The study complies with the declaration of Helsinki.

Informed consent Patient had informed signed consent before the CMR study.

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