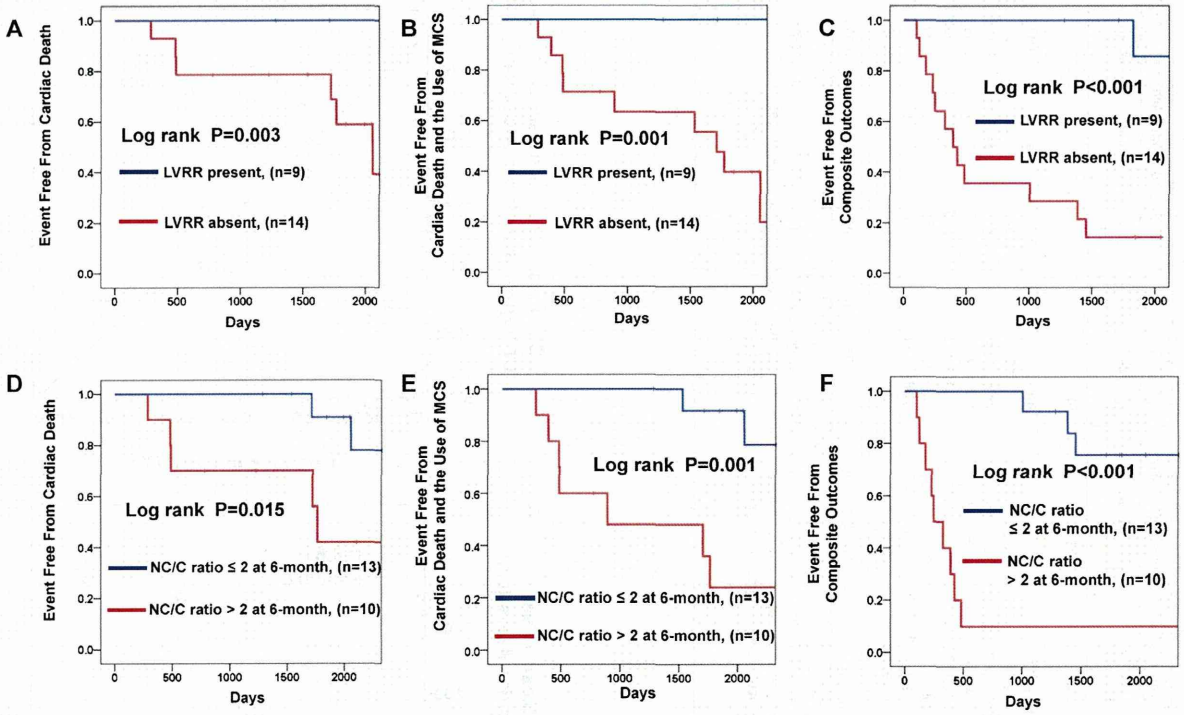

Fig. 4. Kaplan–Meier curves for (A) cardiac death, (B) cardiac death and the use of MCS, and (C) composite outcomes according to the presence of LVRR. Kaplan–Meier curves for (D) cardiac death, (E) cardiac death and the use of MCS, and (F) composite outcomes according to the maximum ratio of the non-compacted to the compacted layer in the left ventricular myocardium. Composite outcomes were cardiac death, the use of mechanical circulatory support, and hospitalization of heart failure. LVRR, left ventricular reverse remodeling; MCS, mechanical circulatory support; NC/C, the non-compacted to the compacted layer.

some patients with heart failure who have been subjected to an increased cardiac preload, as described in our study.

The major complications of LVNC are heart failure, arrhythmia, thromboembolic events, and sudden cardiac death [22,23]. However, little is known about the etiology, diagnostic criteria, incidence, or clinical outcomes associated with LVNC in adults [2]. In our study of adult patients with LVNC appearance, cardiac death occurred in 7 patients (30%) during a follow-up period of 61 months. Oechslin et al. reported the characteristics and outcomes in 34 adults with LVNC, among whom there were 12 deaths (35%) during a follow-up period of 44 months [5]. This was similar to our results.

Previous studies of patients with LV systolic dysfunction found that LVRR in those patients is associated with a favorable prognosis [24–27]. Merlo et al. reported that LVRR in idiopathic dilated cardiomyopathy patients was found in 89 of 242 patients (37%) and patients with LVRR showed a better prognosis compared to those without LVRR during 110 months [24]. However, there are no data regarding the relationship between LVRR and prognosis in patients with LVHT. In our study, patients with LVRR showed a better prognosis compared to those without LVRR, and this phenomenon is similar to those in patients with dilated cardiomyopathy. A recent report about the prognostic impact of LVHT in patients with dilated cardiomyopathy demonstrated that the cardiovascular events did not appear to be influenced by the degree of LVHT at baseline [28]. In our study, there was no difference in the degree of LVHT between the patients with LVRR and without at baseline. Therefore, it is difficult to elucidate the prognosis for cardiovascular events only in terms of the baseline LVHT degree. We firstly demonstrated that the regression of the LVHT, assessed by changes in NC/C ratio and LVHT area, during the follow-up period had a clinical impact on cardiovascular events in patients with LVHT.

Jenni's echocardiographic criterion, namely a NC/C ratio of >2 obtained at end-systole in a parasternal short-axis view, is the most commonly used criterion for the detection of LVNC [10,29–31]. It has previously been validated against dilated cardiomyopathy, hypertensive heart disease, and valvular heart disease and showed good sensitivity and specificity [32,33]. For this reason, we used Jenni's echocardiographic criteria for the selection of the patients in our study.

Our findings demonstrated that some patients showed regression of LVHT, suggesting that LVHT could be reversible. However, it is difficult to reconcile this with the view of LVNC as a primary and genetic cardiomyopathy. Kohli et al. reported that 30 patients (15%) fulfilled Jenni's echocardiographic criteria for LVNC out of 199 patients with LV systolic dysfunction in a single center [4]. This study demonstrated current echocardiographic diagnostic criteria are too sensitive and result in over-diagnosis of LVNC in patients with LV systolic dysfunction as shown in our study. Therefore, we should consider that we might sometimes misclassify a transient cardiomyopathy as LVNC with the use of current morphological criteria alone [7].

Clinical implications

Our study demonstrated that patients without LVRR had a worse prognosis. Patients without LVRR were older and the use of cardiac resynchronization therapy and aldosterone antagonists at 6 months' follow-up was significantly more common than in patients with LVRR. Differences in the patients' characteristics might have been influenced by diagnoses in different phases of the

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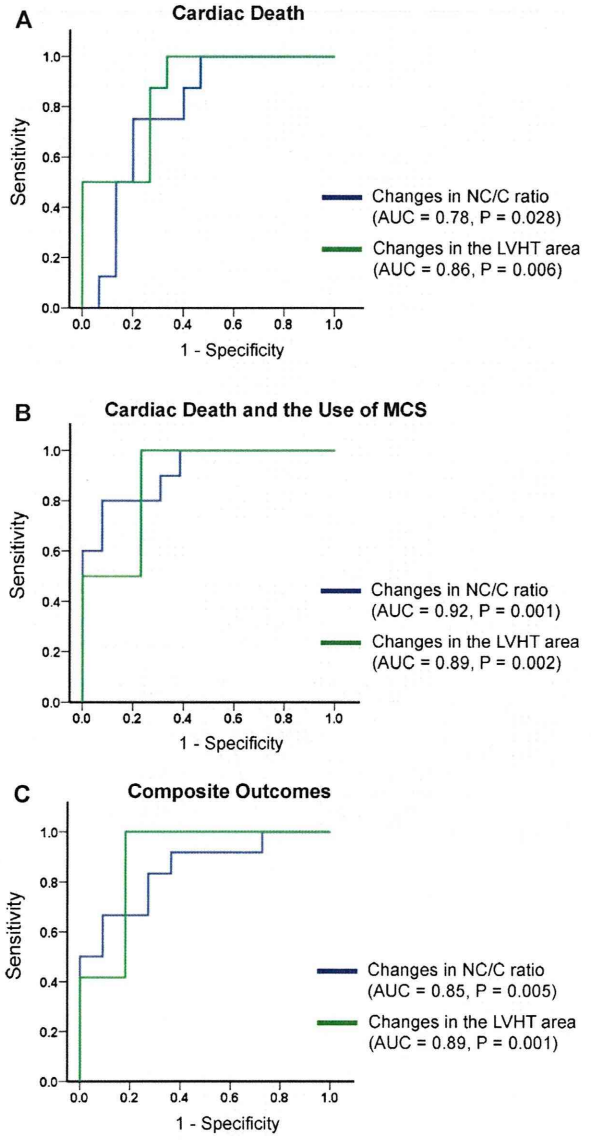

Fig. 5. Receiver-operating characteristic (ROC) curves for predicting (A) cardiac death, (B) cardiac death and the use of MCS, and (C) composite outcomes according to the changes in the maximum ratio of the NC/C in the left ventricular myocardium and the changes in LVHT area from baseline to 6 months' follow-up. Composite outcomes were cardiac death, the use of mechanical circulatory support, and hospitalization of heart failure. LVHT area, left ventricular hypertrabeculation area; MCS, mechanical circulatory support; NC/C, the non-compacted to the compacted layer.

disease (lead-time bias) and have influenced the clinical course in our study. Therefore, the high adverse outcome rate in patients without LVRR necessitates early recognition and appropriate therapeutic intervention, such as the optimal timing of cardiac transplantation referral in patients without LVRR.

Study limitations

The major limitation of our study was being an observational single center study with a small number of subjects; thus our results should be interpreted cautiously until verified in large-scale multicenter studies. We could not perform propensity matched survival analysis and multivariate regression analysis adjusting for confounding factors, including age, and treatment agents because the small number of patients in each group would not be favorable for the above statistical approach. Therefore, it is hard to justify that improved functional and clinical outcomes are related to LVRR in our study. Second, no other cardiac imaging modalities for the quantification of LVHT or myocardial fibrosis, such as cardiac magnetic resonance imaging, were used. We could not perform cardiac magnetic resonance imaging because some patients with LVHT already had cardiac resynchronization therapy devices implanted. Third, our study did not allow speculation about the pathophysiology of the regression of LVHT and the prediction of LVRR. Indeed, we did not analyze the changes in LV mass and regional LV systolic function using 2D echocardiography. It was difficult to elucidate the changes in LV mass because there was no appropriate measurement of LV myocardium mostly in the non-compacted layer. Fourth, endomyocardial biopsy from the right ventricle was performed in 20 patients mostly one time. We might be unable to exclude completely inflammatory cardiac diseases during the follow-up period. Despite these limitations, our findings provide new insight into the relationship between the regression of LVHT, improvement in cardiac systolic function, and prognosis in patients with LVHT, which may be compatible with the diagnosis of LVNC. It remains unclear whether the presence of LVHT is sufficient to explain the influence of clinical outcomes in adult patients with LVHT compared to those in patients without LVHT. Further large-scale multicenter studies are needed to confirm the prognostic significance of regression of LVHT in patients with LV systolic dysfunction and to also perform multivariate analysis to identify factors that predict patient prognosis.

Conclusions

Regression of LVHT is associated with improvement in LV systolic function, and might be associated with a favorable prognosis in patients with LVHT who fulfill the echocardiographic criteria for LVNC.

Conflicts of interest

No conflicts of interest in this study.

References

[1] Arbustini E, Weidemann F, Hall JL. Left ventricular noncompaction: a distinct cardiomyopathy or a trait shared by different cardiac diseases? J Am Coll Cardiol 2014;64:1840–50.
[2] Ikeda U, Minamisawa M, Koyama J. Isolated left ventricular non-compaction cardiomyopathy in adults. J Cardiol 2015;65:91–7.
[3] Ichida F. Left ventricular noncompaction. Circ J 2009;73:19–26.
[4] Kohli SK, Pantazis AA, Shah JS, Adeyemi B, Jackson G, McKenna WJ, Sharma S, Elliott PM. Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? Eur Heart J 2008;29:89–95.
[5] Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 2000;36:493–500.
[6] Cortez-Dias N, Varela MG, Sargento L, Brito D, Almeida A, Cerqueira R, Lança V, Fernandes AR, Tavares P, Pereira RA, Fernandes A, Madeira H. Left ventricular non-compaction: a new mutation predisposing to reverse remodeling? Rev Port Cardiol 2009;28:185–94.
[7] Stöllberger C, Keller H, Finsterer J. Disappearance of left ventricular hypertrabeculation/noncompaction after biventricular pacing in a patient with polyneuropathy. J Card Fail 2007;13:211–4.
[8] Wong PH, Fung JW. Regression of non-compaction in left ventricular non-compaction cardiomyopathy by cardiac contractility modulation. Int J Cardiol 2012;154:e50–1.
[9] Eurlings LW, Pinto YM, Dennert RM, Bekkers SC. Reversible isolated left ventricular non-compaction? Int J Cardiol 2009;136:e35–6.
[10] Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart 2001;86:666–71.

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[11] Kimura K, Takenaka K, Ebihara A, Uno K, Morita H, Nakajima T, Ozawa T, Aida I, Yonemochi Y, Higuchi S, Motoyoshi Y, Mikata T, Uchida I, Ishihara T, Komori T, et al. Prognostic impact of left ventricular noncompaction in patients with Duchenne/Becker muscular dystrophy—prospective multicenter cohort study. Int J Cardiol 2013;168:1900–4.
[12] Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, Silverman NH, Tajik AJ. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
[13] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group. et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
[14] Kusunose K, Yamada H, Nishio S, Tomita N, Hotchi J, Bando M, Niki T, Yamaguchi K, Taketani Y, Iwase T, Soeki T, Wakatsuki T, Sata M. Index-beat assessment of left ventricular systolic and diastolic function during atrial fibrillation using myocardial strain and strain rate. J Am Soc Echocardiogr 2012;25:953–9.
[15] Govindan M, Kiotsekoglou A, Saha SK, Borgulya G, Bajpai A, Bijnens BH, Sagnella G, Camm JA. Validation of echocardiographic left atrial parameters in atrial fibrillation using the index beat of preceding cardiac cycles of equal duration. J Am Soc Echocardiogr 2011;24:1141–7.
[16] Stöllberger C, Blazek G, Gessner M, Bichler K, Wegner C, Finsterer J. Age-dependency of cardiac and neuromuscular findings in adults with left ventricular hypertrabeculation/noncompaction. Am J Cardiol 2015;115:1287–92.
[17] Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008;29:1283–9.
[18] JCS Joint Working Group. Guidelines for treatment of acute heart failure (JCS 2011): digest version. Circ J 2013;77:2157–201.
[19] JCS Joint Working Group. Guidelines for non-pharmacotherapy of cardiac arrhythmias (JCS 2011): digest version. Circ J 2013;77:249–74.
[20] Kubanek M, Sramko M, Maluskova J, Kautznerova D, Weichet J, Lupinek P, Vrbska J, Malek I, Kautzner J. Novel predictors of left ventricular reverse remodeling in individuals with recent-onset dilated cardiomyopathy. J Am Coll Cardiol 2013;61:54–63.
[21] Gati S, Papadakis M, Papamichael ND, Zaidi A, Sheikh N, Reed M, Sharma R, Thilaganathan B, Sharma S. Reversible de novo left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular non-compaction in low risk populations. Circulation 2014;130:475–83.
[22] Ichida F, Hamamichi Y, Miyawaki T, Ono Y, Kamiya T, Akagi T, Hamada H, Hirose O, Isobe T, Yamada K, Kurotobi S, Mito H, Miyake T, Murakami Y, Nishi T, et al. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. J Am Coll Cardiol 1999;34:233–40.
[23] Peters F, Khandheria BK, Botha F, Libhaber E, Matioda H, Dos Santos C, Govender S, Meel R, Essop MR. Clinical outcomes in patients with isolated left ventricular noncompaction and heart failure. J Card Fail 2014;20:709–15.
[24] Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. J Am Coll Cardiol 2011;57:1468–76.
[25] de Groote P, Fertin M, Duva Pentiah A, Goéminne C, Lamblin N, Bauters C. Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after β-blocker therapy. Circ Heart Fail 2014;7:434–9.
[26] Choi JO, Kim EY, Lee GY, Lee SC, Park SW, Kim DK, Oh JK, Jeon ES. Predictors of left ventricular reverse remodeling and subsequent outcome in nonischemic dilated cardiomyopathy. Circ J 2013;77:462–9.
[27] Kainuma S, Taniguchi K, Toda K, Shudo Y, Takeda K, Funatsu T, Miyagawa S, Kondoh H, Nishi H, Yoshikawa Y, Fukushima S, Hamada S, Kubo K, Daimon T, Sawa Y. B-type natriuretic peptide response and reverse left ventricular remodeling after surgical correction of functional mitral regurgitation in patients with advanced cardiomyopathy. J Cardiol 2015;66:279–85.
[28] Amzulescu MS, Rousseau MF, Ahn SA, Boileau L, de Meester de Ravenstein C, Vancraeynest D, Pasquet A, Vanoverschelde JL, Pouleur AC, Gerber BL. Prognostic impact of hypertrabeculation and noncompaction phenotype in dilated cardiomyopathy: a CMR Study. JACC Cardiovasc Imaging 2015;8:934–46.
[29] Gebhard C, Stähli BE, Greutmann M, Biaggi P, Jenni R, Tanner FC. Reduced left ventricular compacta thickness: a novel echocardiographic criterion for non-compaction cardiomyopathy. J Am Soc Echocardiogr 2012;25:1050–7.
[30] Paterick TE, Umland MM, Jan MF, Ammar KA, Kramer C, Khandheria BK, Seward JB, Tajik AJ. Left ventricular noncompaction: a 25-year odyssey. J Am Soc Echocardiogr 2012;25:363–75.
[31] Caselli S, Autore C, Serdoz A, Santini D, Musumeci MB, Pelliccia A, Agati L. Three-dimensional echocardiographic characterization of patients with left ventricular noncompaction. J Am Soc Echocardiogr 2012;25:203–9.
[32] Greutmann M, Mah ML, Silversides CK, Klaassen S, Attenhofer Jost CH, Jenni R, Oechslin EN. Predictors of adverse outcome in adolescents and adults with isolated left ventricular noncompaction. Am J Cardiol 2012;109:276–81.
[33] Agarwal A, Khandheria BK, Paterick TE, Treiber SC, Bush M, Tajik AJ. Left ventricular noncompaction in patients with bicuspid aortic valve. J Am Soc Echocardiogr 2013;26:1306–13.

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