Peer Review File

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Reviewer 1

1. Late gadolinium enhancement might be related to the cause of mitral regurgitation. Therefore, authors should be analyzed the relation between late gadolinium enhancement and the cause of mitral regurgitation.

Response: Thanks for your suggestion, and it is important for this paper. In our series of patients with LVNC, there was no incremental association between the grade of MR and the frequency of LGE+. However, in the moderate–severe MR group, LGE was associated with mortality, which is possibly due to the superimposed effect of LGE and moderate–severe MR. LV maladaptive remodeling may be caused by chronic pressure or volume overload, or to an intrinsic myocardial weakness such as a genetic defect. LV myocardial fibrosis is an advanced step of LV remodeling. LGE by CMR revealed myocardial fibrosis. While secondary MR may be caused of LV dysfunction, mitral annular dilation, or both. Therefore, we speculate that MR was not directly associated with the presence of LGE. Mild MR has less effect on cardiac morphology, but moderate and severe MR can lead to varying degrees of changes in cardiac structure and function. Our research also showed that as the degree of MR increased, LV remodeling became more severe, and LV function worsened. But in the moderate–severe MR group, LGE was associated with mortality, which is possibly due to the combined effect of LGE and moderate–severe MR. Since both fibrosis and moderate-severe MR are related to the occurrence and development of myocardial remodeling, they may have a superimposed effect on the occurrence of MACE. However, whether there is an interaction between the amount of regurgitation and replacement myocardial fibrosis detected by CMR in patients with LVNC is unknow according current research. In the future, we will expand the number of cases and make exploration for association between these two parameters, which is very meaningful. We added the related discussed in the discussion section which on line 346 - 362.

2. The names of mitral regurgitation + group and mitral regurgitation – group are difficult to understand. The authors should change the names.

Response: We are very sorry for the confusion caused by the name of each group. We have changed the name of the group to "No MR, Mild MR, Moderate-severe MR". And we have modified the name of group in the manuscript.

3. Authors should describe left atrial size in Table 3.

Response: Thanks for your suggestion. We have added the data of left atrial antero-posterior diameter (LAAPD) and transverse diameters (TD) in Table 3. LAAPD was measured by the vertical distance from the farthest point of the posterior wall of the LA to the atrial septum on the three-chamber cine image at the LA end-diastolic phase. LATD was measured on the four-chamber cine image, which should be measured perpendicular to the LA length. Related description has been added to the methods section of the manuscript. (line 175 - line 180)

4. Page 5, lines 72-73. The authors should describe the result of the log-rank test.

Response: We are very sorry for inaccurate description of the result. And related description has been correct in manuscript. (line 72-73 and line 239)

Reviewer 2

1. This is clearly a very small sample of NCLV at large. You represent that this is a general study of NCL as diagnosed by Petersen criteria. This may be incorrect to state! Specigcally, your population is of patients not general population (likely, they were referred to your centers because CHF symptoms or signs). Your entry is from a prior diagnositic process/database that you cannot define or control at this point, I guess. In reality, Petersen criteria of a general population will report that those criteria are positive in 18% or so of a large population of adolescents (you may quote Angelini et al 2018 at: https://doi.org/Texas Heart Institute Journal • August 2018, Vol. 45, No. 4

10.14503/THIJ-18-6645). If you should apply the same prevalence data (unsure at your group's age and functional class to require CMR), the expected number of NCLV (with any LVEF) would have been 2.244! (your sample is probably 3.3% of the truly total, but I am not sure of a Chinese population).

Response: Thank you so much for your suggestions, which are very meaningful and helpful! As you say, this study is a retrospective cohort study. We retrospectively analyzed the basic information, CMR and echocardiographic findings of patients in different groups from the clinical, CMR and echocardiographic databases, and followed up the prognosis of patients. we extracted consecutive patients who had CMR reports that included descriptions of noncompaction or hypertrabeculation or cardiomyopathy. All diagnoses were made by two experienced radiologists. After all the cases were extracted, the images were reanalyzed, measured and grouped by two other radiologists, who were blinded to the clinical data. Disagreements, if any, were resolved by consensus including a third expert. Related description has been added to the methods section of the manuscript. (line 116 - line 122)

However, there is selection bias in our study, which is emphasized in the limitation section. As all these three centers are tertiary-care referral centers, most patients had been treated in local hospitals for a period of time before they come to our hospital for examination. Most of them were in seriously condition with varying degrees of decreased myocardial function. Similar observations were reported by Cheng H et al.(1) Of all our enrolled patients, only 13 (17.3%) of LVNC patients had myocardial function greater than 50%.

2. In reality, you did not include data from a screening population study but from somebody else radiologists' diagnosis was entered your database. Wouldn't agree? Most of your patients apparently had DCM of some severity, jointly with NCLV, and I am not sure why some patients could be entered, but having normal or mildly depressed LVEF... or 45% mean LVEF, but no MR. Please, in Table3 clarify that LV mass was calculated only about LV compact mass (excluding NC). Please, in Table3 clarify that LV mass was calculated only about LV compact mass (excluding NC).

Response: Thank you for your advice. Since patients only came from these three hospitals, our positive rate was affected by selection and referral biases when using Petersen Criteria, which may be inconsistent with literature reports. Moreover, we have added the inclusion criteria in the methods section on the line 130 that “All patients included in our research were adults (≥18 years), with any LVEF”. LV mass was calculated only about LV compact mass (excluding NC) in our research. And related description has been added to the methods section of the manuscript (line 175) and Table 3.

3. Line 90: "LVNC is mainly defined by the NC layer". Actually, currently it seems that the most important parameter for severity in LVNC is the description of LV compact layer (it seems thinner than the rest, underneath NC hypertrabeculations (data in publication). But you did not analyse most of the NCLV who have normal LVEF (99% of cases of NCLV by Petersen criteria have a normal LVEF).

Response: Thank you for your comments. LVNC is a heterogeneous cardiomyopathy, described as excessive myocardial trabeculation and deep inter-trabecular recesses. NC layer is only one of the main imaging characteristics of LVNC. One important parameter of LVNC diagnosis is NC/C measured at end-diastole. Actually, LV compact layer is the very important part in LVNC, because this part is important for maintaining the structure and function of the myocardia. The original sentence has been revised in the manuscript. (line 90-92)

4. You state that MR is "frequent in NCLV", but you should limit your statement by including "NCLV with LV dysfunction" have high incidence of MR. The "garden variety of NCLV has normal LV function and very rare MR.

Response: Thanks for your suggestion! This description is indeed more accurate. The prevalence of isolated LVNC in various studies differs significantly and clinical presentation is rather heterogeneous, ranging from subclinical forms to overt symptoms and even cardiac death. While the average myocardial function of the patients we included was low, as you say, which cannot represent all LVNC patients, especially

LVNC patients with normal myocardial function. And the original sentence has been revised in the manuscript (line 382-383).

5. line 116: You did not screen 12,469 general population cases, but you entered 75 cases diagnosed by others, from a database that you did not apparently revise personally, for this study. (my guess)

Response: This study is a retrospective cohort study. We retrospectively analyzed the basic information and MRI, echocardiographic findings of patients from the clinical and CMR, echocardiographic databases, and followed up the prognosis of some patients. we extracted consecutive patients who had CMR reports that included descriptions of noncompaction or hypertrabeculation or cardiomyopathy. All diagnoses were made by two experienced radiologists. Therefore, although the authors did not personally review every report in the case system, we fully trust the description and conclusions of the original reports. For the clearly diagnosed cases, the images were reanalyzed, measured and grouped by two radiologists, who were blinded to the clinical data. (line 116-122)

6. line 123. How would you define "other CMP"?

Response: The other primary cardiomyopathy inclusive of congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, cardiac amyloidosis, or sarcoidosis. We identified and excluded them by analyzing the clinical database and CMR and echocardiographic image features. We have added description of other CMP in the manuscript on line 128 -129.

7. line 139. How many cross-sections did you select in each patient (6 to 12, every 10 or 8 mm thick?).

Response: Thank you for your comments.. In our study, A balanced steady-state free precession (bSSFP) sequence was used to acquire 8 -12 continuous cine images from

the base to the apex. And related description has been added to the methods section of the manuscript on line 144 - 145.

8. Line 143. Define how to diagnose LGE-myocardial scar in NCLV? I guess only in compact layers.

Response: Thank you for your comments. LGE was visually assessed on short-axis image in compact layers. The long-axis images were used to confirm the presence of LGE. Increased signal in deep intertrabecular recesses caused by the blood cistern signal may lead to misdiagnosis of LGE. Thus, we only diagnose LGE-myocardial scar in compact layers. we have added the related description in the methods section on line 185 - 187.

9. Line 151. Usually, clinical diagnosis of severity in MR in cardiomyopathies requires indices of diastolic disfucntion and pulmonary pressure. Please, discuss this likely limitation.

Response: Thanks for your suggestion. This was one of the limitations in our research. “Color flow jet area” was used for assessing MR severity in our study. Clinically, this is a simple and quick screen method widely used in the evaluation of MR severity. However, this method has certain limitations when diagnosing severe MR, especially when the MR jet is eccentric. At this time, we will assess whether there is left atrial and/or ventricular dilation or with swirling jet or reversal of flow in pulmonary veins to confirm the diagnosis of severe MR in our research. However, as our research was a retrospective study that had a long time span (from 2013 to 2020), when we retrospectively collected echocardiographic data, diastolic dysfunction and pulmonary arterial pressure parameters could not be obtained and reassessed from every patient. Thus, there may be some deviation in diagnosis of severe MR. In our study, moderate MR and severe MR were combined into a moderate-severe MR group to research and analysis, which may reduce MR diagnostic deviation to some extent by such MR diagnostic method. Related description has been added to the limitation section of the manuscript (line 158-160 and line 372-377).

10. Regarding sphericity index in your patients, this interesting approach has never been reported and it would be proper to it, in this paper. Please, enter detail information at this respect. Normally, investigators assume that NC trabeculations have also some intrisic property that prevents dilatation but produces diastolic dysfunction (increased end-diastolic pressure)

Response: Thank you for your comments. Study by Liang Y et al.(2) showed that Sphericity index (SI) is an independent predictor for clinical outcomes in patients with nonischemic dilated cardiomyopathy, which is useful to reflect LV structural remodeling and disease severity of nonischemic DCM. As SI does not require extra sequence and contrast agent, it maybe a promising parameter for clinical practice. Therefore, we want to explore whether SI has such prognostic value in LVNC patients combined with MR. In our study, SI significantly increased in moderate-severe MR group, indicating that the LV already had obvious morphological changes and became more round and blunt. However, SI did not show significant prognostic value according to both Kaplan-Meier analysis and COX analysis. As there may be potential selection and referral biases in our cohort, this conclusion may not universally applicable to all populations. In the follow-up studies, we will expand the number of cases and make further exploration for this parameter. Related description has been added in the manuscript (line 300-305).

11. Line 201-3. Please emphasize that 28% of your NCLV cases had no MR... with a possibly decreased LVEF.

Response: Thanks for your suggestion, which is very useful. And related description has been correct in manuscript. (line 208-209)

12. line 207. The mean LVEF in your cohort was 30.9%. How did the institutional radiologists eliminate most of the "normal LVEF patients with positive Petersen's criteria" from being diagnosed NCLV?

Response: Thank you for your comments. All the images were evaluated and diagnosed

by two radiologists with more than 3 years of diagnostic experience. However, all of the data are from the hospitals which are tertiary-care referral centers in China. That's mean most of patients clinically referred for echocardiography and CMR investigation already had dramatic symptoms. A large number of studies have shown that clinically asymptomatic LVNC with normal LVEF had better prognosis, which is well known by many doctors in clinical practice. Therefore, the majority of LVNC patients with normal LVEF are often not present at these referral centers, and most of them had TTE test with normal LVEF and without further CMR. So, a lot of people with normal ejection fractions are not in our cohort, causing potential selection referral biases.

13. Line 271. please, correct "staining" (it probably meant " strain").

Response: Thanks for the reminder. We had corrected the description in manuscript. (line 288)

14. Line 304. LVEF did not significantly correlate with worse outcomes: if this is correct, it would imply that in NCLV the presence of NC layer could prevent the evolution of DCM (by preventing LV dilatation?).

Response: Thank you for your comments, and I thought it is an interesting consideration. Our results only showed that LVEF had no significant predictive value for MACE in the LVNC patients with MR. However, this does not mean that LVEF has no predictive value for MACE in the overall LVNC patients. Moreover, study indicated that the relationship between LVEF and survival probability was weaker when LVEF < 25%(3). Actually, other studies(4, 5) on the LVNC with different groups had shown that LVEF was associated with MACE. But the hypothesis you put forward was very interesting, which would be further discussed in the future research. In this study, we could not explanation whether in NCLV the presence of NC layer could prevent the evolution of DCM by preventing LV dilatation, but I think it can be verified by the necessary animal study or a better prospectively design in the further.

15. LGE is a robust predictor MACE: I am not sure that this was proven in NCLV

(versus in Coronary artery disease or myocarditis). Please, clarify that LGE scar is limited to compact layer scars: in the NC layer there are plenty of scars...

Response: Thanks for your suggestion! Increased signal in deep intertrabecular recesses caused by the blood cistern signal may lead to misdiagnosis of LGE, cause the signal of blood pool, which has shorter T1 time, may mimic scar tissue. Thus, the diagnosis of LGE is limited to compact layer. And related description has been revised in the manuscript (line 186-187). And for the predictive value of LGE for the MACE in LVNC patients, there were several studies have shown positive results and a meta-analysis about prognostic role of LGE in LVNC also showed that LGE is associated with worse prognosis in patients with LVNC independent of LVEF(4-6).

16. "...coronary microcirculation..." Use please a quote of this concept, if available. Probably you imply that scars in CMP are due to small vessels disease... Unclear.

Response: Thanks for your comment! Actually, the LGE assessed by CMR may be the result of a series of pathological mechanisms such as coronary microcirculation, inflammation, edema, fiber hyperplasia, et al. The cause of myocardial fibrosis may be possibly associated with small vessels disease, as you mentioned, including diminished coronary flow reserve, impaired microcirculatory function, coronary artery embolism in previous(7-10). The presentation in the section of the manuscript were not rigorous. We have modified the description on line 358-360.

Reference:

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