Review

Magnetic resonance diagnostic criteria of non-compaction cardiomyopathy: new diagnostic criteria still needed?

Karolina Gaižauskienė [a,*], Gabrielė Glembockytė [b], Sigita Glaveckaitė [c], Nomeda Rima Valevičienė [a]

[a] *Department of Radiology, Nuclear Medicine and Medical Physics, Institute of Biomedical Sciences, Vilnius University Faculty of Medicine, Vilnius, Lithuania; Radiology and Nuclear Medicine Centre, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania*

[b] *Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

[c] *Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Vilnius University Faculty of Medicine, Vilnius, Lithuania; Centre for Cardiology and Angiology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania*

Received 20 June 2022; accepted 5 December 2022

Summary

Non-compaction cardiomyopathy (NCC) is a rare pathology, but the exact rates of its prevalence are not known due to the lack of a diagnostic gold standard. The purpose of this article is to analyse the available cardiovascular magnetic resonance (CMR) diagnostic criteria of non-compaction described in the literature and to compare their sensitivity and specificity in the diagnosis of NCC. A search of available literature related to the CMR diagnostic criteria of myocardial non-compaction was conducted in the medical database PubMed in February of 2022. The period of publication of scientific articles covered the years from 1996 to 2022. A total of 7 full-text scientific articles were included in the final literature review. The main diagnostic criteria were used: the maximum non-compact (NCM) to compact myocardial layers (CM) ratio (NCM:CM), the percentage of trabeculated left ventricular (LV) myocardial mass, the percentage of trabeculated LV myocardial volume, the non-compact myocardial mass index of the total LV, and the determination of the total LV and the maximal fractal dimension (FD) of the apex with the use of fractal analysis. The lack of accurate diagnostic criteria results in an overdiagnosis of NCC. The highest sensitivity and specificity are associated with the maximum FD > 1.30 of the apex established by applying the fractal analysis method. Fractal analysis requires dedicated software, and this method is difficult to apply in routine clinical practice. Thus, the diagnostic criteria for the NCC using magnetic resonance imaging with higher diagnostic value remain to be sought.

Seminars in Cardiovascular Medicine 2023; 29:1–13

Keywords: non-compaction cardiomyopathy, cardiac magnetic resonance imaging, diagnostic criteria

Introduction

Non-compaction cardiomyopathy (NCC) is a structural and functional disorder of the myocardium characterized by a two-layer myocardium, thickening of the muscle wall, increased trabeculation, and the formation of deep pockets between trabeculae. Most commonly, changes are noticed in the left ventricular myocardium, especially at the apex; however, isolated non-compaction of the right ventricle or both ventricles may also occur [1]. Non-compact myocardium consists of the outer compact epicardial layer and the inner, usually thicker, non-compact endocardial layer [2]. For the description of non-compaction cardiomyopathy, literature sources use synonyms – "non-compaction of the left ventricular (LV) myocardium" or "left ventricular non-compaction cardiomyopathy", and for the characterization of the phenotype, the synonym "hypertrabeculation" is used [3].

NCC is a rare pathology, but the exact rates of its prevalence are not known due to the lack of a diagnostic gold standard [4]. According to the most recent studies, the frequency ranges from 1.28% to 14.79%, depending on the method of imaging test used, research subjects, and the

* Corresponding address: Karolina Gaižauskienė, Radiology and Nuclear Medicine Centre, Vilnius University Hospital Santaros Klinikos, Santariškių str. 2, LT-08661 Vilnius, Lithuania
Phone: +37069771003
E-mail: karolina.lusaite@santa.lt.

diagnostic criteria applied [5]. Non-compaction of the myocardium is more common in males and the ethnic groups of African Americans and Latin Americans [6–8]. In children, NCC occurs in 0.11 out of 100 000 and in 9.2% of cases where cardiomyopathy is diagnosed before the age of 10 years [9]. The manifestations of the clinical symptoms caused by non-compact myocardium can range from completely asymptomatic disease to severe complications – systemic embolic events, life-threatening conduction abnormalities, heart failure, and sudden cardiac death [2, 10]. Non-compaction of the myocardium may manifest as an isolated, primary myocardial disorder, or as a pathological process in addition to various cardiac diseases (such as hypertrophic or dilated cardiomyopathies), congenital heart disease, or neuromuscular disease, further complicating the diagnosis of NCC [11]. Due to the heterogeneity of the disease, there is no universally accepted classification for the non-compaction of the LV myocardium. According to the guidelines of the American Heart Association, the pathology is classified as primary genetic cardiomyopathy, however, based on the classification of the European Society of Cardiology, it is attributed to unclassified cardiomyopathies due to common phenotypic manifestation of other cardiomyopathies [12,13].

The formation of trabeculae is associated with a normal phase in myocardial development that ensures cardiac function and the exchange of oxygen and metabolism in the myocardium during embryogenesis [14]. However, the exact aetiology of pathological trabeculation and non-compaction is not known, meanwhile, various studies describe several theories explaining the origin of NCC. One of the main theories highlights an intensified formation of trabeculae, myocardial compaction disorder, and the difference in the rates of the development of myocardial compaction and trabeculae during embryogenesis [4]. Another theory talks about gene mutations that cause damage to the genes for sarcomere (contractile elements) and cytoskeletal proteins genes, which are mostly detected in the TTN (titin protein) gene [1,15,16]. Also, significantly increased myocardial trabeculation is noticed in certain specific groups of individuals. With increasing cardiac preload and cardiac output, myocardial remodelling intensifies, and adaptive mechanisms promote pathological endocardial trabeculation in patients with heart failure [4, 17]. Physiological hypertrabeculation, which is potentially reversible, can be detected in pregnant women or physically active individuals [18, 19]. Due to the similar morphological expression and unclear aetiology, it is difficult to distinguish actual cardiomyopathy from phenotypic manifestations of adaptive myocardial mechanisms in healthy individuals, leading to diagnostic difficulties and excessive diagnosis of NCC [5].

Non-compact myocardium is diagnosed based on the results of cardiac imaging tests. Several methods can be used for diagnosis: transthoracic echocardiography, cardiac magnetic resonance imaging (CMR), and, less commonly, cardiac computed tomography [20,21]. Although there is no unanimously accepted non-compaction diagnostic gold standard, one of the main criteria used in the clinical practice are the echocardiographic criteria described by Jenni et al. in 2001: the ratio of non-compact to compact myocardial layers (NCM:CM) is greater than 2 at the end of systole, the non-compaction of myocardium is expressed in the localizations typical for this pathology, the colour Doppler method shows blood flow in the intertrabecular pockets, and no concomitant cardiac disorders are found in the patient [22,23]. However, despite the simplicity and widespread use of echocardiography, the present study distinguished in low reproducibility of the test results, it is difficult to visualize the apex of the cardiac myocardium, which is one of the most common sites of myocardial trabeculation, and the sensitivity of these echocardiographic criteria is only up to 64% [24,25]. CMR, compared to transthoracic echocardiography, is a superior technique which provides additional information on cardiac morphology and more accurately assesses the extent of non-compact myocardium, thus allowing better sensitivity in respect of NCC diagnosis [26]. According to the data of the recent systematic review and meta-analysis, non-compact myocardium is detected 12 times more frequently in different patient groups when applying CMR comparing to the use of echocardiographic criteria [5]. Thus, the improved diagnostic capabilities of CMR to detect non-compact myocardium increase the likelihood of a false-positive results in healthy individuals [4]. There are still no specific and generally accepted criteria for the diagnosis of non-compact myocardium when applying CMR that allow distinguishing phenotypic non-compaction of myocardium from the diagnosis of a life-altering cardiomyopathy with sufficient accuracy. For these reasons, the analysis of the diagnostic criteria of non-compact myocardium is important to determine which diagnostic plan might be most appropriate to confirm the diagnosis of NCC as accurately as possible.

The purpose of this article is to analyse the available CMR based diagnostic criteria of myocardial non-compaction described in the litera-

ture and to compare their sensitivity and specificity in the diagnosis of this pathology.

Strategy for search of literature sources

A search of literature sources related to the criteria for the diagnosis of non-compact myocardial magnetic resonance imaging was conducted in the medical database PubMed in February 2022. The search was performed by entering a combination of definitions in English – *left ventricular* AND *noncompaction* OR *non-compaction* AND *magnetic resonance imaging* AND *diagnostic*. The period of publication of scientific articles was not limited and covered the years from 1996 to 2022.

Selection of literature sources and data acquisition

The analysis of literature sources included scientific articles written in English, the full text of which was available in the PubMed database. Upon identification of articles according to the search definitions, the duplicate publications were removed. The selection of literature sources was carried out in two phases. In the first phase, a review of the title and summary of the article was performed. Articles were included in the full-text review phase based on the following inclusion criteria:

1. Studies examining the diagnostic criteria for non-compact myocardial magnetic resonance imaging.
2. Adolescents and adults as the target group of a study (patients of 10 years of age or older).
3. Type of a study – retrospective or prospective research.
4. Studies describing patients from any country in the world.
5. Studies the full text of which is available for review.

A full-text analysis of the selected studies was performed after reviewing the title and summary. Articles whose title and summary did not provide sufficient information to assess the inclusion criteria were also included in this phase, when it was believed that an article was likely to be suitable for the literature review. The suitability of the studies for the literature review after the full-text analysis was assessed based on the following exclusion criteria:

1. Descriptions of a single clinical case, review studies.
2. Patients under 10 years of age were included in the study.
3. Studies describing the diagnostic criteria for tests other than magnetic resonance imaging.
4. Studies whose diagnostic criteria were applied only to persons with concomitant pathology.
5. Studies without threshold values for specific diagnostic criteria.
6. Studies the contents of which did not correspond to the researched topic (only magnetic resonance diagnostic criteria supplementing the diagnosis were analysed).

The main data for the literature review were collected from scientific articles: the author of an article, title, year of publication, country, study type, number and groups of subjects, age, criteria for inclusion in a NCC study, diagnostic criteria provided by the authors, and their sensitivity and specificity. Also, the study parameters: the scanning plane and the phase of the cardiac cycle in which the measurements were performed.

Titles and abstracts of 535 publications in total were evaluated after primary literature search and removal of duplicate publications. 501 articles were rejected based on the inclusion criteria. In the next phase of selection, a full-text analysis of 34 scientific articles was performed. Of these, 27 publications were excluded from the literature review based on the exclusion criteria, the main reasons being the irrelevant type of study and the lack of specific diagnostic criteria. A total of 7 full-text scientific articles were included in the final literature review. The period of publication of these articles covered the years from 2005 to 2016. A detailed selection scheme for the search of scientific articles is presented in Figure 1.

All studies selected for literature analysis were retrospective. The sample of patients who were suspected of having NCC included in the study ranged from 7 to 122. The age of the patients who participated in the study ranged from 11 to 74.5 years. In six of the seven studies, control groups of healthy subjects were included. In addition, to assess the diagnostic value of the NCC criteria to differentiate NCC from other pathologies, various population groups characterized by increased LV myocardial trabeculation were selected. Patients with hypertrophic and dilated cardiomyopathies, hypertensive disease, aortic valve stenosis or regurgitation, and healthy and physically active individuals were included in the final analysis. The study by Stacey et al. did not exclude a control group of healthy subjects – all the subjects were included in the group of the suspected NCC [27]. Data on the main characteristics of the studies included in the literature review are provided in Table 1.

Due to the lack of a gold standard for NCC, selection criteria were identified in each study.

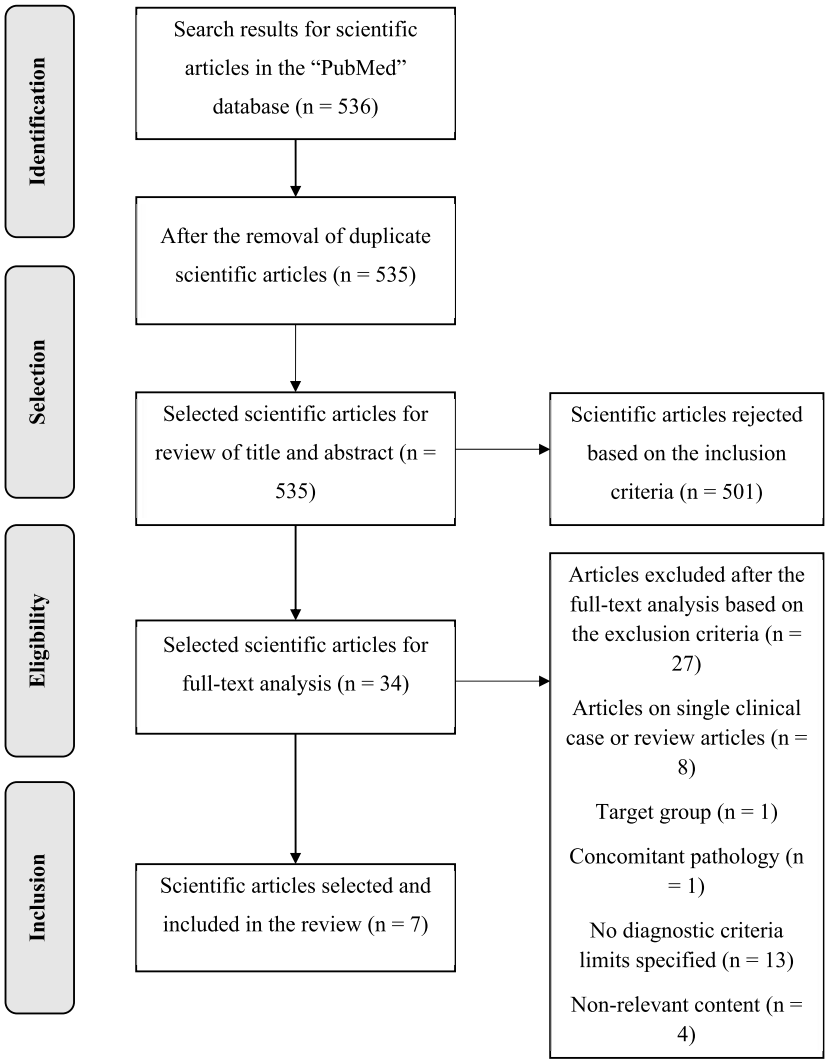

Figure 1. Scheme of selection of scientific articles.

In general, patients were selected for the studies based on echocardiographic or CMR imaging analysis of LV non-compact myocardium. Echocardiographic criteria for diagnosis of non-compact myocardium established in the studies by Jenni et al. were used in four of the seven literature review studies as selection criterion [23,29–32]. The selection criteria defined in the study by Petersen et al. – documented two-layerness of trabeculated myocardium as assessed by echocardiography or CMR, but no specific threshold for myocardial non-compaction was determined [28]. In the study by Stacey et al., from a group of patients who underwent CMR for various cardiological reasons, cases with documented signs of trabeculated myocardium or non-compaction of myocardium were selected retrospectively [27]. In the study by Choi et al., patients were selected according to the criteria provided by Petersen et al. – myocardial two-layerness and the NCM:CM ratio in diastole >2.3 [33]. In order to increase the diagnostic yield of NCC, three studies defined additional criteria for inclusion in the studies: a family history, an associated neuromuscular disorder, or a clinical presentation of complications caused by non-compaction of myocardium [28, 31,32]. Detailed NCC selection criteria for the study are provided in Table 2.

Diagnostic criteria established by Petersen et al. [28]

According to Petersen et al., the diagnosis of non-compact myocardium requires two criteria. In particular a clear morphological sign of two-layered myocardium, consisting of a compact epicardial and a non-compact endocardial layer, must be confirmed using CMR. The second criterion is the NCM:CM ratio >2.3 when assessing the highest ratio established in the diastole. The maximum NCM:CM ratio is measured on any of the long axes in the CMR images at the end of diastole. The apex of the heart (segment 17) is not included in the measurements due to the physiologically thinner compact myocardial

Table 1.
Main characteristics of the studies included in the literature review of the diagnostic CMR criteria for NCC.

No.	First author, year	Country	Type of study	Sample (n)	Patient groups	Age
1.	Petersen et al., 2005 [28]	United Kingdom	Retrospective	n = 177	NCC (n = 7) DCM (n = 14) HCM (n = 39) HHD (n = 17) AoS (n = 30) Athletes (n = 25) Control (n = 45)	14–46 years
2.	Jacquier et al., 2010 [29]	France	Retrospective	n = 64	NCC (n = 16) HCM (n = 16) DCM (n = 16) Control (n = 16)	31–65 years
3.	Cheng et al., 2011 [30]	China	Retrospective	n = 145	NCC (n = 28) DCM (n = 45) HHD (n = 19) AoS (n = 16) AR without stenosis (n = 15) Control (n = 22)	29.3–59.5 years
4.	Grothoff et al., 2012 [31]	Germany	Retrospective	n = 57	NCC (n = 12) DCM (n = 11) HCM (n = 10) Control (n = 24)	11–71 years
5.	Captur et al., 2013 [32]	United Kingdom	Retrospective	n = 135	NCC (n = 30) Control, White race (n = 75) Control, Black race (n = 30)	28–54 years
6.	Stacey et al., 2013 [27]	USA	Retrospective	n = 122	–	39.5–74.5 years
7.	Choi et al., 2016 [33]	South Korea	Retrospective	n = 145	NCC (n = 24) Not isolated NCC (n = 33) DCM + NCC (n = 30) DCM + H (n = 27) Control + H (n = 31)	38.4–71.6 years

Abbreviations: AR – aortic regurgitation; AoS – aortic stenosis; DCM – dilated cardiomyopathy; H – hypertrabeculation; HCM – hypertrophic cardiomyopathy; HHD – hypertensive heart disease; NCC – non-compaction cardiomyopathy; n – number of patients.

layer of the apex. The NCM:CM ratio in the NCC group was on average 60% higher ($p < 0.01$) compared to the other study groups. The number of non-compact myocardial segments (10 ± 3) was found to be statistically significantly larger ($p < 0.01$) in the group of pathological myocardial non-compaction compared to other groups of participants. The criteria established by Petersen et al. are easily applied in clinical practice and have a high specificity (99%), however, the sample of patients who participated in the study was relatively small (n = 7) to allow a reliable assessment of the diagnostic value of the criteria [28].

Diagnostic criteria established by Jacquier et al. [29]

The diagnostic criterion for non-compact myocardium established by Jacquier et al. is the percentage of the LV trabeculated myocardium mass equal to or more than 20% of the total mass of the LV myocardium. Measurements are performed on short-axis CMR images at the end of diastole. It was found that the criterion of the myocardial mass of trabeculated LV confirms the diagnosis of NCC with a sensitivity and specificity of 93.7% if the selection criteria established by Jacquier et al. are acceptable as a gold standard. If only the criteria established by Jenni et al. are used for the NCC sampling, then the sensitivity and specificity of the trabeculated LV myocardial mass criterion are lower, 91.6% and 86.5%, respectively. The main disadvantage of this criterion is that when measuring the percentage part of trabeculated myocardium, the part of the blood pool in the area of the trabeculated myocardium is included in the measurements, which may lead to inaccurate measurements [29].

Table 2.
NCC diagnostic criteria used in the studies included in the literature review

No.	First author, year	NCC diagnostic criteria for inclusion in the study
1.	Petersen et al., 2005 [28]	Characterization of two-layer myocardium on echocardiography or CMR and one of the following criteria: • Clinical presentation of NCC in first-degree relatives; • Associated neuromuscular disorder; • Complications: systemic embolic events or segmental cardiac wall motion disturbances.
2.	Jacquier et al., 2010 [29]	12 patients were selected according to the echocardiographic criteria established by Jenni et al.[1] 4 patients were selected according to the signs of echocardiographic two-layer myocardium and >3 prominent trabeculae and family history of NCC.
3.	Cheng et al., 2011 [30]	According to the echocardiographic criteria established by Jenni et al.[1]
4.	Grothoff et al., 2012 [31]	Echocardiographic criteria established by Jenni et al.[1] and one of the following criteria: • Suspected/confirmed NCC in first-degree relatives; • Associated neuromuscular disorder; • Complications: systemic embolic events and/or segmental cardiac wall motion disturbances or ventricular tachycardia with/without syncope.
5.	Captur et al., 2013 [32]	Echocardiographic criteria established by Jenni et al.[1] and one of the following criteria: • Positive family history; • Associated neuromuscular disorder; • Segmental cardiac wall motion disturbances; • Complications: arrhythmias, heart failure, thromboembolism.
6.	Stacey et al., 2013 [27]	Trabeculation or non-compaction of myocardium documented by using CMR.
7.	Choi et al., 2016 [33]	A clear sign of two-layer myocardium on CMR by using criteria established by Petersen et al. (28)

Abbreviations: CMR – cardiac magnetic resonance; NCC – non-compaction cardiomyopathy.
Explanations: [1] NCC echocardiographic diagnostic criteria established by Jenni et al. [23]:

1. No concomitant cardiac anomalies.
2. A two-layer myocardial structure composed of a compact thin epicardial layer, and a significantly thicker non-compact endocardial layer composed of a trabeculated mesh with deep endomyocardial recesses, with a maximum ratio of non-compact to compact myocardial layers >2 at the end of the systole.
3. Non-compaction of myocardium predominates in the apical, infero-lateral midventricular segments of the LV myocardium.
4. Blood flow in intertrabecular recesses is determined by using the colour Doppler method.

Diagnostic criteria established by Cheng et al. [30]

The study by Cheng et al. compared the sensitivity and specificity of several NCM:CM ratio threshold values when confirming the diagnosis of NCC. The study found that the highest sensitivity (96.4%) and specificity (97.4%) were noticed in the presence of the NCM:CM ratio >2.5 at the end of diastole in short-axis CMR images. The NCC group showed a statistically significant ($p < 0.001$) higher maximum of the NCM:CM ratio compared to the other study groups. Based on the results of the study, the maximum NCM:CM ratio >2 is 100% sensitive for the detection of the non-compaction of myocardium in CMR imaging but showed low specificity of 67.5%. The sensitiv-

ity of the criterion of the maximum NCM:CM ratio >2.3 was higher, but the specificity was lower than that reported by Petersen et al. However, it should be noted that the measurements were performed on different axes [28]. In the study, the apex of the heart was not included in the measurements due to the physiologically thinner compact layer. The main disadvantage of the study was that the study was performed including only the Chinese population [30].

Diagnostic criteria established by Grothoff et al. [31]

Diagnosis of non-compact myocardium by Grothoff et al. consists of four diagnostic criteria for non-compact myocardium, with measurements performed on short-axis CMR images at the end of diastole. The mass index of the total myocardial and the myocardial mass of trabeculated LV differed statistically significantly from other cardiomyopathies and healthy subjects ($p < 0.001$). The optimal threshold values for the diagnosis of NCC are presented in the results of the study – the mass index of the total LV non-compact myocardium >15 g/m^2 and the mass of trabeculated LV myocardium >25% of the total LV mass. Two of the four criteria were based on the segmental NCM:CM ratio of $\geq$3 in at least one of segments 1–3 and 7–16, excluding the apex, and the NCM:CM ratio $\geq$4–6 in the base segments, due to their higher incidence of the non-compaction of myocardium in the patients of the NCC group. Although the result of the study provides the sensitivity and specificity of the individual diagnostic criteria for the diagnosis of NCC, the best results are determined by evaluating all four diagnostic criteria altogether. All four criteria have a sensitivity of 75% and a specificity of 100% [31].

Diagnostic criteria established by Captur et al. [32]

Diagnostic criteria established in other studies mentioned in the literature review are based on the morphological measurements of the cardiac myocardium, such as the NCM:CM ratio, and the mass or volume of trabeculated myocardium. The study performed by Captur et al. measured the endocardial with the use of the fractal analysis method magnetic resonance imaging in the short-axis images of the heart at the end of diastole (Figure 2) [32]. Fractal analysis is a method for quantitative estimation of complex geometric models. The result is expressed in terms of the fractal dimension (FD) – a dimensionless measurement index that shows how structure fills a space in a complex way. Because a trabeculated endocardial edge is more complex and less regular than the straight line, FD >1 is determined, however, the edge never fills the two-dimensional cross-sectional structure of the CMR which means that there will always be <2. The study by Captur et al. presents two diagnostic criteria: the total LV FD and the maximum FD of the apex and their diagnostic thresholds. The >1.26 indicator of the total LV FD confirms pathological trabeculated myocardium of LV with 83% sensitivity and 86% specificity. An even more sensitive and specific criterion is the maximal FD of the apex, which was statistically significantly different from healthy groups of the study ($p <0.00001$). The maximum FD >1.30 of the apex was characterized by 100% sensitivity and specificity for confirmation of the NCC diagnosis. Disadvantages of the study: only one feature of NCC magnetic resonance imaging was considered – trabeculation, however, other features typical to this pathology, such as thinning of the compact myocardial layer, were not considered. Knowledge of mathematical fractals is required to analyse this indicator in CMR imaging for NCC diagnostic purposes [32].

Diagnostic criteria established by Stacey et al. [27]

The diagnostic criterion for non-compact myocardium established by Stacey et al. is based on the NCM:CM ratio greater than or equal to 2 when measuring the short-axis CMR images. This ratio is the lowest compared to other studies included in the literature review and, unlike other NCM:CM ratios, the measurements of diagnostic criteria are made at the end of systole rather than diastole. The study does not provide the sensitivity and specificity of the NCM:CM diagnostic criterion $\geq$2 in the diagnosis of NCC; therefore, these criteria cannot be compared with other diagnostic criteria. However, the results of the study showed that the threshold value of the NCM:CM ratio of $\geq$2, when measured at the end of systole rather than diastole, has a stronger association with the LV function than with the NCM:CM ratio of >2.3 measured at the end of diastole. The patients with the NCM:CM threshold of $\geq$2 have been established to have a higher incidence of heart failure (odds ratio 29.4; 95% CI 6.6-125) and other clinical events related to NCC such as ventricular arrhythmias, embolic events, and repeated hospitalization for heart failure (odds ratio 8.6; 95% confidence interval 2.5–33) [27].

Diagnostic criteria established by Choi et al. [33]

The main criterion established by Choi et al. is the measured trabeculated LV myocardial volume of >35% of the total LV myocardial volume

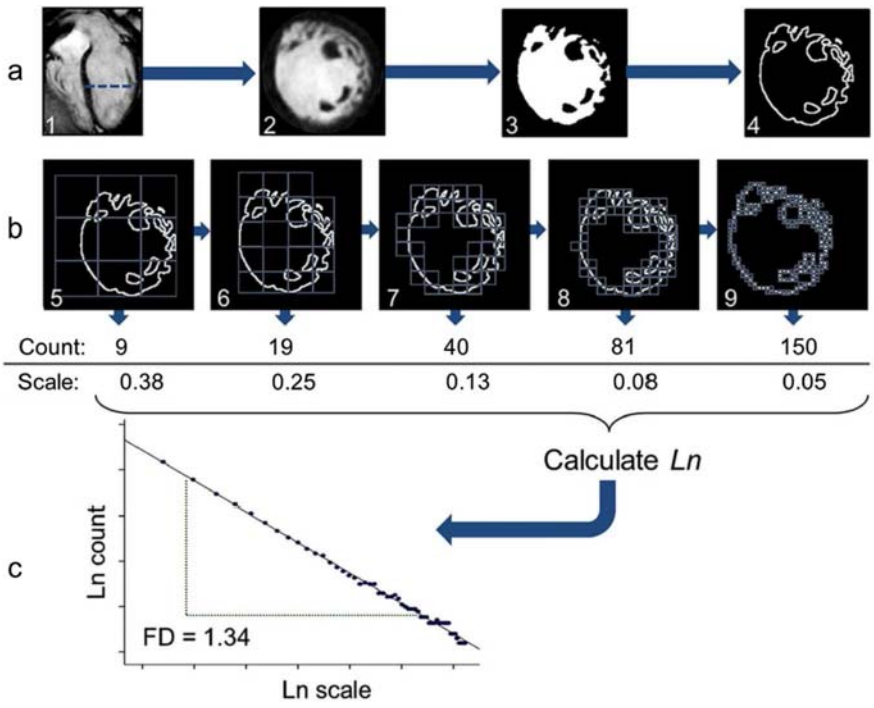

Figure 2. Image processing sequence and fractal analysis of left ventricular cine images. Reproduced from Captur et al. [32].

when measuring on the short axis of cardiac magnetic resonance imaging at the end of diastole. Compared to the results of the diagnostic criteria presented in other studies, the criterion of trabeculated myocardial volume established by Choi et al. has the lowest sensitivity (66.1%) provided the diagnostic criteria established by Jenni et al. are considered to be the gold standard. The study also describes and supplements the criteria for the diagnosis of non-compact myocardium when the compact myocardial layer of LV at the apex of the heart cannot be measured. The ratio of trabeculated myocardium to compact myocardial in the lateral segments of the apex, greater than 3.15, was 69.5% sensitive and 93.1% specific when diagnosing NCC. Another criterion described is that greater than 1.27 ratio of the thickness of the non-compact myocardium to the wall thickness of the middle septum. The sensitivities and specificities described for this criterion were 57.6% and 82.8%, respectively. Measurements of additional criteria were performed on the long axes in diastole [33].

The four studies included in the literature review used the maximum NCM:CM ratio as the main diagnostic criterion. In two studies, the percentage of trabeculated LV myocardial mass was used, while in one study, the percentage of trabeculated LV myocardial volume. The studies also described the non-compact myocardial mass index of the total LV and the determination of the total LV and the maximum FD of the apex with the use of a fractal analysis. In most studies, the measurements of the main diagnostic criteria were performed in cardiac short-axis magnetic resonance imaging. The only study by Petersen et al. provided criteria for measurements on any longitudinal axis of the heart [28]. Although measurements were made at the end of diastole in six of the seven studies, the results of the study by Stacey et al. showed that systolic measurements provide prognostic insights [27]. All magnetic resonance imaging diagnostic criteria analysed in the literature review are applicable to the diagnosis of cardiomyopathy induced by the non-compact myocardium of LV and their sensitivity and specificity have not been studied for the assessment of the non-compaction of the right ventricle. The highest sensitivity of the magnetic resonance diagnostic criterion was established in the study by Captur et al. The maximum fractal dimension >1.30 of the apex was measured with the use of fractal analysis and was found to be 100% sensitive when confirming the diagnosis [32]. The most specific diagnostic criteria were given in the results of the study by Grothoff et al. and Captur et al. – the diagnosis can be made with 100% specificity by applying all four diagnostic criteria of non-compact myocardial magnetic resonance imaging established by Grothoff et al., as well as the diagnostic criteria of the maximum fractal dimension >1.30 of the apex established by Captur et al. [31,32]. In addition, a high 99% specificity was established for the NCM:CM ratio of >2.3 in the study performed by Petersen et al. [28].

In summary, all magnetic resonance imaging diagnostic criteria described in the literature review have their own advantages and disadvantages that are difficult to compare between studies, however, the most sensitive and specific in diagnosing NCC is the maximum FD of the LV apex of >1.30 as measured in cardiac short-axes at the end of diastole [32]. A detailed summary of the results of the literature review of non-compact myocardial magnetic resonance diagnostic criteria is provided in Table 3.

Discussion

Application of diagnostic criteria

The present review of the literature shows that modern NCC diagnostics in magnetic resonance imaging is based on the results of small-sample, mostly single-centre studies. Due to the lack of a gold standard, the authors of the studies selected different criteria for the inclusion which, in their opinion, define the NCC diagnosis most accurately; therefore, it can be stated that the results of these studies may differ after applying magnetic resonance diagnostic criteria in the clinical practice. The inaccuracies in the diagnostic criteria for non-compact myocardial magnetic resonance imaging described in the literature are also confirmed by the results of large-sample studies that show that the current diagnostic criteria are false-positive in a large proportion of asymptomatic individuals without clinically significant adverse outcomes [34]. For example, one study in which the study group corresponded to the general population, evaluated the CMR diagnostic NCC criteria established by Petersen et al., Grothoff et al. (NCM:CM $\geq$3), Stacey et al. and Jacquier et al. [27–29,31,35]. The results showed that 62.8%, 35.8%, 22% and 20.6% of the study participants, respectively, met the listed criteria, and 14.8% of the participants had at least one of the analysed NCC diagnostic criteria, while 1.3% of the participants met all 4 criteria examined in the research [35]. In another prospective study, the conformity of the magnetic resonance imaging diagnostic criteria established by Petersen et al., Stacey et al., Jacquier et al. and Captur et al. in the sample of cardiac patients were 39%, 23%, 25%, and 3%, respectively, and the NCC diagnosis was not associated with adverse clinical outcomes over a 7-year period [27–29,32,36]. In the school-age population, the non-compact myocardial criteria established by Petersen et al. were confirmed in 18.6% of the study participants, and when followed by evaluation with the use of the criteria of Choi et al., Grothoff et al., the criteria were confirmed in 17.5%, 7.4%, and 1.3% of participants, respectively [28,29,31,33,37,38]. Thus, although the results of the studies were very different, most of them confirm the low specificity of the diagnostic CMR criteria for NCM, applying them to the general or target population.

According to the data of a long-term MESA study (Multi-Ethnic Study of Atherosclerosis), 323 participants without cardiovascular disease, the NCM:CM threshold of >2.3 at the end of diastole established by Petersen et al. was found in as many as 43% of participants in at least one left ventricular region (8 regions were assessed – anterior, inferior, septal, and lateral at mid-ventricular and apical levels at end-diastole), and in 6% of participants this ratio was found in more than 2 regions studied [28,40]. Upon evaluation of the CMR imaging of 2472 subjects in a further analysis of the MESA study data, it was found that the NCM:CM ratio of >2.3 was confirmed in 25.7% of the subjects in whom trabeculated myocardium did not significantly affect LV end-systolic and end-diastolic volumes or LV function changes over a 9.5-year period. Based on these results, in patients meeting diagnostic criteria proposed by Petersen et al., NCC should be diagnosed when there are not only anatomical features of non-compaction but also accompanying clinical symptoms related to NCM [28, 40]. In addition, another MESA study evaluated the complexity of the endocardial layer edge in CMR images with the use of fractal analysis. The results of the study showed that in the group of healthy subjects, the maximal FD of the apex ranged within the limits of 1.169 $\pm$ 0.05, and the established highest maximum FD of the apex, equal to 1.279, was lower than threshold value of >1.30 provided in the study of Captur et al. [8,32]. For these reasons, it can be argued that the FD of >1.30 of the apex reported by Captur et al. is likely to be an accurate magnetic resonance indicator, distinguishing NCC from the trabeculation of a physiological healthy heart [32].

Late gadolinium enhancement in cardiac magnetic resonance imaging

The main morphological feature of NCC is the two-layerness of myocardium; most diagnostic criteria are based on the ratio of non-compact to compact myocardium. However, in addition to this primary feature, magnetic resonance imaging reveals additional myocardial changes. Damage to the myocardium caused by cardiomyopathies, including NCC, manifests as myocardial fibrosis. In magnetic resonance imaging, myocardial fibrosis may be seen in the late gadolinium enhancement (LGE) imaging and is associated with a risk of adverse cardiovascular complications [41,42]. According to the meta-analysis, LGE

Table 3.
Diagnostic value of CMR diagnostic criteria for NCC used in studies included in the literature review

No.	First author, year	Diagnostic criteria	Sensitivity, %	Specificity, %	Cardiac cycle phase	CMR plane
1.	Petersen et al. 2005 [28]	A clear feature of two-layered myocardium is distinguished	86	99	End of diastole	Any image in the long axis
		Maximum NCM:CM >2.3 (the apex is not included in the measurements)				
2.	Jacquier et al., 2010 [29]	Mass of LV trabeculated myocardium is >20% of the total mass of LV	93.7	93.7	End of diastole	Short axis
3.	Cheng et al., 2011 [30]	Maximum NCM:CM is >2.5 (the apex is not included in the measurements)	96.4	97.4	End of diastole	Short axis
4.	Grothoff et al., 2012 [31]	Mass index of the total LV non – compact myocardium (for body surface area) >15 g/m^2	75	100	End of diastole	Short axis
		Mass of non-compact LV myocardium is >25% of the total mass of LV				
		NCM:CM is ≥3 in at least one of segments 1–3 and 7–16				
		NCM:CM ≥2 in segments 4–6				
5.	Captur et al., 2013 [32]	General FD of LV is >1.26	83	86	End of diastole	Short axis
		Maximum FD of the apex is >1.30	100	100		
6.	Stacey et al., 2013 [27]	Maximum NCM:CM is ≥2	–	–	End of systole	Short axis
7.	Choi et al., 2016 [33]	Volume of trabeculated LV myocardium is >35% of the total LV myocardial volume	66.1	89.7	End of diastole	Short axis
		Additional criterion: apex and CM ratio is >3.15	69.5	93.1	Diastole	Long axis
		Additional criterion: NCM and septum ratio is >1.27	57.6	82.8	Diastole	Long axis

Abbreviations: Apex – thickness of trabeculation measured in the apical part of the myocardium; CM – thickness of compact myocardium; CMR – cardiac magnetic resonance imaging; FD – fractal dimension; LV – left ventricle; NCM – thickness of non-compact myocardium; NCM:CM – ratio of non-compact to compact myocardial layers; Septum – wall thickness of the middle part of the septum.

in individuals with signs of non-compact myocardium is associated with a statistically significantly higher overall risk of adverse events (odds ratio 4.9; 95% confidence interval 1.63–14.6; p = 0.005) and cardiac death (odds ratio – 9.8, 95% confidence interval 2.44–39.5, p < 0.001) than for those without LGE [43]. It is known that LGE in CMR is associated with an increased cardiovascular risk in patients with NCC who do not have cardiac dysfunction [44]. Based on these data, LGE could have additional diagnostic and prognostic value along the diagnostic criteria for non-compact myocardial CMR used in the clinical practice.

Non-compact myocardium – a separate type of cardiomyopathy or physiological variation of myocardial morphology?

The large numbers of data of false-positive NCC diagnoses in the studies raise the question of whether this is a consequence of the high sensitivity and low specificity of magnetic resonance imaging diagnostic criteria, or whether non-compact myocardium is a physiological variation of myocardial morphology rather than a

separate type of cardiomyopathy [35]? The magnetic resonance imaging criteria used in practice consider only visual changes in the non-compact myocardium and do not assess the functional changes of LV or additional pathological signs such as myocardial fibrosis [45]. According to data of the studies, the prognostic value of NCC and the incidence of adverse outcomes are more related to LV dilatation, LV systolic dysfunction, and the presence of late gadolinium enhancement than the presence of myocardial hypertrabeculation [46–48]. In addition, the prognosis for subjects with NCC is the same as for subjects without signs of non-compact myocardium, taking into account that the LV ejection fraction is the same [43]. In addition, excessive myocardial trabeculation over a one-year period was not associated with an increased incidence of cardiovascular morbidity and overall patient mortality [34]. This observation confirms that morphological features of hypertrabeculation alone in CMR imaging are not an indicator of clinically poor prognosis, and the assessment of the LV function could be one of the auxiliary diagnostic features of magnetic resonance imaging seeking to distinguish cardiomyopathy from adaptive myocardial changes.

Another way to confirm the diagnosis of non-compact myocardium and assess the prognostic value of hypertrabecularization could be the identification of genetic mutations that cause cardiomyopathy. In 20–40% of NCC cases, the diagnosis of hereditary non-compact myocardium is confirmed, and as much as 43 pathogenic gene variants have been established that lead to the manifestation of the non-compactness of myocardium [49]. The currently known mutations of the genes that determine NCC are independently associated with an increased risk of death and heart transplantation in adults [16]. It has been established that some of the positive prognostic indicators associated with probable pathogenic NCC gene variants are: diagnosis of hereditary cardiomyopathy, larger trabeculation mass and the magnetic resonance imaging criterion of NCM:CM ratio >2.3 confirmed by Petersen et al. along with the positive family history [28,50]. When applying the criteria for the diagnosis of magnetic resonance non-compact myocardium to probable pathogenic gene variants, it was revealed that the highest level of conformity was found in the criteria by Petersen et al. (97%), while the lowest level was found in the criteria by Stacey et al. (47%) [27,28,50]. However, due to the low specificity of magnetic resonance criteria in the general population demonstrated in previous studies, the diagnostic value of these indicators is questionable. However, the NCC genotype has not been adequately studied yet and the absence of known pathogenic variants does not exclude the diagnosis of cardiomyopathy, therefore further studies are needed to elucidate in detail the added value of genetic testing in the diagnosis of NCC.

Limitations of the review

The search of the articles included in the review of literature on non-compact myocardial magnetic resonance imaging criteria was performed in a single database, therefore it may be the case that some studies have not been included in the review. In addition, the diagnostic criteria for non-compact myocardial magnetic resonance imaging analysed in the review were studied in the adolescent and adult populations and their application in the paediatric population is not known because studies involving subjects under 10 years of age had been intentionally excluded. In addition, the application of the magnetic resonance diagnostic criteria analysed is possible only for the diagnosis of LV non-compact myocardium; these criteria are not applied in the assessment of the non-compactness of the right ventricular myocardium.

Conclusions

The current diagnostic criteria for non-compaction cardiomyopathy are based on the results of retrospective small and single centre studies. The modern practice has no gold standard for the diagnosis of NCC by using cardiac magnetic resonance imaging, and the diagnostic criteria used in the clinical practice have low specificity. The lack of accurate diagnostic criteria results in an overdiagnosis of NCC in a large proportion of healthy individuals with adaptive hypertrabecularization. Of all the diagnostic criteria used in magnetic resonance imaging described in this article, the highest sensitivity and specificity, as well as the probability of accurately distinguishing non-compact myocardial cardiomyopathy from adaptive myocardial changes, is associated with the maximum fractal dimension of >1.30 of the apex established by applying the by fractal analysis method in the cardiac short-axis imaging at the end of diastole. Fractal analysis requires dedicated software, and this method is difficult to apply in routine clinical practice. Thus, the diagnostic criteria for magnetic resonance imaging myocardial non-compact cardiomyopathy with higher diagnostic value remain to be sought.

Implication for clinical practice

Looking for more accurate CMR diagnostic criteria of NCC, multicentre, large-scale studies are needed which could help to distinguish NCC from physiological, non-life threatening increased in myocardial trabeculation. Modern diagnostic criteria of NCC should include more than just morphological changes. Cardiac functional and structural changes as assessed by using CMR, as well as other clinical and genetical data, should be evaluated to avoid overdiagnosis of NCC.

References

[1] Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet Lond Engl* 2015;386(9995):813–25.

[2] Towbin JA, Jefferies JL. Cardiomyopathies due to left ventricular noncompaction, mitochondrial and storage diseases, and inborn errors of metabolism. *Circ Res* 2017;121(7):838–54.

[3] Gerecke BJ, Engberding R. Noncompaction cardiomyopathy – history and current knowledge for clinical practice. *J Clin Med* 2021;10(11):2457.

[4] D'Silva A, Jensen B. Left ventricular non-compaction cardiomyopathy: how many needles in the haystack? *Heart* 2021;107(16):1344–52.

[5] Ross SB, Jones K, Blanch B, Puranik R, McGeechan K, Barratt A, et al. A systematic review and meta-analysis of the prevalence of left ventricular non-compaction in adults. *Eur Heart J* 2020;41(14):1428–36.

[6] Kayvanpour E, Sedaghat-Hamedani F, Gi WT, Tugrul OF, Amr A, Haas J, et al. Clinical and genetic insights into non-compaction: a meta-analysis and systematic review on 7598 individuals. *Clin Res Cardiol Off J Ger Card Soc* 2019;108(11):1297–308.

[7] Caine A, Franzil J, Milks W, Upadhya B, Hundley G, Stacey B. Racial differences in left ventricular trabeculations by cardiac magnetic resonance imaging. *J Am Coll Cardiol* 2015;65(10_Supplement):A1094–A1094.

[8] Captur G, Zemrak F, Muthurangu V, Petersen SE, Li C, Bassett P, et al. Fractal analysis of myocardial trabeculations in 2547 study participants: multi-ethnic study of atherosclerosis. *Radiology* 2015;277(3):707–15.

[9] Rath A, Weintraub R. Overview of cardiomyopathies in childhood. *Front Pediatr* 2021;9:708732.

[10] Ikeda U, Minamisawa M, Koyama J. Isolated left ventricular non-compaction cardiomyopathy in adults. *J Cardiol* 2015;65(2):91–7.

[11] Filho DCS, do Rêgo Aquino PL, de Souza Silva G, Fabro CB. Left ventricular noncompaction: new insights into a poorly understood disease. *Curr Cardiol Rev* 2021;17(2):209–16.

[12] Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies. *Circulation* 2006;113(14):1807–16.

[13] Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European society of cardiology working group on myocardial and pericardial diseases. *Eur Heart J* 2008;29(2):270–6.

[14] Wengrofsky P, Armenia C, Oleszak F, Kupferstein E, Rednam C, Mitre CA, et al. Left ventricular trabeculation and noncompaction cardiomyopathy: a review. *EC Clin Exp Anat* 2019;2(6):267–83.

[15] Zhou D, Li S, Sirajuddin A, Wu W, Huang J, Sun X, et al. CMR characteristics, gene variants and long-term outcome in patients with left ventricular non-compaction cardiomyopathy. Insi*ghts Imaging* 2021;12(1):184.

[16] Li S, Zhang C, Liu N, Bai H, Hou C, Wang J, et al. Genotype-positive status is associated with poor prognoses in patients with left ventricular noncompaction cardiomyopathy. *J Am Heart Assoc* 2018;7(20):e009910.

[17] Di Toro A, Giuliani L, Smirnova A, Favalli V, Serio A, Urtis M, et al. Myths to debunk: the non-compacted myocardium. *Eur Heart J Suppl J Eur Soc Cardiol* 2020;22(Suppl L):L6–10.

[18] Oechslin E, Jenni R. Left ventricular noncompaction. *J Am Coll Cardiol* 2018;71(7):723–6.

[19] Gati S, Rajani R, Carr-White GS, Chambers JB. Adult left ventricular noncompaction: reappraisal of current diagnostic imaging modalities. *JACC Cardiovasc Imaging* 2014;7(12):1266–75.

[20] Chebrolu LH, Mehta AM, Nanda NC. Noncompaction cardiomyopathy: The role of advanced multimodality imaging techniques in diagnosis and assessment. *Echocardiography* 2017;34(2):279–89.

[21] Fuchs TA, Erhart L, Ghadri JR, Herzog BA, Giannopoulos A, Buechel RR, et al. Diagnostic criteria for left ventricular non-compaction in cardiac computed tomography. *PLoS ONE* 2020;15(7):e0235751.

[22] Srivastava S, Yavari M, Al-Abcha A, Banga S, Abela G. Ventricular non-compaction review. *Heart Fail Rev* 2022;27(4):1063-1076

[23] 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 Br Card Soc* 2001;86(6):666–71.

[24] Rao K, Bhaskaran A, Choudhary P, Tan TC. The role of multimodality imaging in the diagnosis of left ventricular noncompaction. *Eur J Clin Invest* 2020;50(9):e13254.

[25] Mavrogeni SI, Markousis-Mavrogenis G, Vartela V, Manolopoulou D, Abate E, Hamadanchi A, et al. The pivotal role of cardiovascular imaging in the identification and risk stratification of non-compaction cardiomyopathy patients. *Heart Fail Rev* 2020;25(6):1007–15.

[26] Thuny F, Jacquier A, Jop B, Giorgi R, Gaubert JY, Bartoli JM, et al. Assessment of left ventricular non-compaction in adults: side-by-side comparison of cardiac magnetic resonance imaging with echocardiography. *Arch Cardiovasc Dis* 2010;103(3):150–9.

[27] Stacey RB, Andersen MM, St Clair M, Hundley WG, Thohan V. Comparison of systolic and diastolic criteria for isolated LV noncompaction in CMR. *JACC Cardiovasc Imaging* 2013;6(9):931–40.

[28] Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* 2005;46(1):101–5.

[29] Jacquier A, Thuny F, Jop B, Giorgi R, Cohen F, Gaubert JY, et al. Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. *Eur Heart J* 2010;31(9):1098–104.

[30] Cheng H, Zhao S, Jiang S, Yu J, Lu M, Ling J, et al. Cardiac magnetic resonance imaging characteristics of isolated left ventricular noncompaction in a Chinese adult Han population. *Int J Cardiovasc Imaging* 2011;27(7):979–87.

[31] Grothoff M, Pachowsky M, Hoffmann J, Posch M, Klaassen S, Lehmkuhl L, et al. Value of cardiovascular MR in diagnosing left ventricular non-compaction cardiomyopathy and in discriminating between other cardiomyopathies. *Eur Radiol* 2012;22(12):2699–709.

[32] Captur G, Muthurangu V, Cook C, Flett AS, Wilson R, Barison A, et al. Quantification of left ventricular trabeculae using fractal analysis. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 2013;15:36.

[33] Choi Y, Kim SM, Lee SC, Chang SA, Jang SY, Choe YH. Quantification of left ventricular trabeculae using cardiovascular magnetic resonance for the diagnosis of left ventricular non-compaction: evaluation of trabecular volume and refined semi-quantitative criteria. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 201618(1):24.

[34] Zemrak F, Raisi-Estabragh Z, Khanji MY, Mohiddin SA, Bruder O, Wagner A, et al. Left ventricular hypertrabeculation is not associated with cardiovascular morbity or mortality: insights from the EuroCMR registry. *Front Cardiovasc Med* 2020;7:158.

[35] Weir-McCall JR, Yeap PM, Papagiorcopulo C, Fitzgerald K, Gandy SJ, Lambert M, et al. Left ventricular noncompaction: anatomical phenotype or distinct cardiomyopathy? *J Am Coll Cardiol* 2016;68(20):2157–65.

[36] Ivanov A, Dabiesingh DS, Bhumireddy GP, Mohamed A, Asfour A, Briggs WM, et al. Prevalence and prognostic significance of left ventricular noncompaction in patients referred for cardiac magnetic resonance imaging. *Circ Cardiovasc Imaging* 2017;10(9):e006174.

[37] Angelini P, Cheong BY, Lenge De Rosen VV, Lopez A, Uribe C, Masso AH, et al. High-risk cardiovascular conditions in sports-related sudden death: prevalence in 5,169 schoolchildren screened via cardiac magnetic resonance. *Tex Heart Inst J* 2018;45(4):205–13.

[38] Masso AH, Uribe C, Willerson JT, Cheong BY, Davis BR. Left ventricular noncompaction detected by cardiac magnetic resonance screening: a reexamination of diagnostic criteria. *Tex Heart Inst J* 2020;47(3):183–93.

[39] Kawel N, Nacif M, Arai AE, Gomes AS, Hundley WG, Johnson C, et al. Trabeculated (non-compacted) and compact myocardium in adults: The Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2012;5(3):357–66.

[40] Zemrak F, Ahlman MA, Captur G, Mohiddin SA, Kawel-Boehm N, Prince MR, et al. The relationship of left ventricular trabeculation to ventricular function and structure over a 9.5-year follow-up: the MESA study. *J Am Coll Cardiol* 2014;64(19):1971–80.

[41] Schiau C, Schiau Ş, Dudea SM, Manole S. Cardiovascular magnetic resonance: contribution to the exploration of cardiomyopathies. *Med Pharm Rep* 2019;92(4):326–36.

[42] Nucifora G, Aquaro GD, Pingitore A, Masci PG, Lombardi M. Myocardial fibrosis in isolated left ventricular non-compaction and its relation to disease severity. *Eur J Heart Fail* 2011;13(2):170–6.

[43] Grigoratos C, Barison A, Ivanov A, Andreini D, Amzulescu MS, Mazurkiewicz L, et al. Meta-analysis of the prognostic role of late gadolinium enhancement and global systolic impairment in left ventricular noncompaction. *JACC Cardiovasc Imaging* 2019;12(11 Pt 1):2141–51.

[44] Casas G, Limeres J, Oristrell G, Gutierrez-Garcia L, Andreini D, Borregan M, et al. Clinical risk prediction in patients with left ventricular myocardial noncompaction. *J Am Coll Cardiol* 2021;78(7):643–62.

[45] Arbustini E, Favalli V, Narula N, Serio A, Grasso M. Left ventricular noncompaction: a distinct genetic cardiomyopathy? *J Am Coll Cardiol* 2016;68(9):949–66.

[46] Aung N, Doimo S, Ricci F, Sanghvi MM, Pedrosa C, Woodbridge SP, et al. Prognostic significance of left ventricular noncompaction. *Circ Cardiovasc Imaging* 2020;13(1):e009712.

[47] Andreini D, Pontone G, Bogaert J, Roghi A, Barison A, Schwitter J, et al. Long-term prognostic value of cardiac magnetic resonance in left ventricle noncompaction: a prospective multicenter study. *J Am Coll Cardiol* 2016;68(20):2166–81.

[48] Femia G, Zhu D, Choudhary P, Ross SB, Muthurangu V, Richmond D, et al. Long term clinical outcomes associated with CMR quantified isolated left ventricular non-compaction in adults. *Int J Cardiol* 2021;328:235–40.

[49] Ichida F. Left ventricular noncompaction – Risk stratification and genetic consideration. *J Cardiol* 2020;75(1):1–9.

[50] van Waning JI, Caliskan K, Chelu RG, van der Velde N, Pezzato A, Michels M, et al. Diagnostic cardiovascular magnetic resonance imaging criteria in noncompaction cardiomyopathy and the yield of genetic testing. *Can J Cardiol* 2021;37(3):433–42.