

Native T1 time and extracellular volume fraction in differentiation of normal myocardium from non-ischemic dilated and hypertrophic cardiomyopathy myocardium: A systematic review and meta-analysis

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ABSTRACT

Background: Both native T1 time and extracellular volume (ECV) fraction have been shown to be important measures for the detection of myocardial fibrosis. However, ECV determination requires the administration of an intravenous contrast agent, whereas native T1 mapping can be performed without a contrast agent.

Methods: Here, we conducted a meta-analysis of myocardial native T1 data obtained for non-ischemic cardiomyopathy (NIC) patients and controls. A literature review included studies that applied T1 mapping using modified Look-Locker inversion recovery to measure myocardial fibrosis, and the results were validated by comparing datasets for dilated cardiomyopathy (DCM) or hypertrophic cardiomyopathy (HCM) patients and healthy controls (HCs).

Results: We identified 16 eligible studies. Pooled mean differences (MDs) and 95% confidence intervals (CIs) were estimated as follows. Native T1 at 1.5-T, DCM vs. HC: MD = 45.26 (95% CI: 30.92–59.59); HCM vs. HC: MD = 47.09 (95% CI: 32.42–61.76). Native T1 at 3.0-T, DCM vs. HC: MD = 82.52 (95% CI: 47.60–117.44); HCM vs. HC: MD = 115.87 (95% CI: 50.71–181.04). ECV at 1.5-T, DCM vs. HC: MD = 4.26 (95% CI: 3.06–5.46); HCM vs. HC: MD = 1.49 (95% CI: –1.45–4.43). ECV at 3.0-T, DCM vs. HC: MD = 8.40 (95% CI: 2.94–13.86); HCM vs. HC: MD = 8.02 (95% CI: 5.45–1–0.59).

Conclusion: In conclusion, native T1 values were significantly different between NIC patients and controls. Native T1 mapping may be a useful noninvasive method to detect diffuse myocardial fibrosis in NIC patients.

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Abbreviations: CI, confidence interval; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ECV, extracellular volume; HC, healthy control; HCM, hypertrophic cardiomyopathy; LGE-MRI, late gadolinium-enhanced magnetic resonance imaging; MD, mean difference; MINORS, Methodological Index for Non-Randomized Studies; MOLL, modified Look-Locker inversion recovery; NIC, non-ischemic cardiomyopathy; SCD, sudden cardiac death; SD, standard deviation.

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1. Introduction

Myocardial fibrosis is a pathological hallmark of non-ischemic cardiomyopathy (NIC). Cardiac magnetic resonance (CMR) enables non-invasive quantification of myocardial fibrosis in NIC patients. Late gadolinium enhancement magnetic resonance imaging (LGE-MRI) is an established CMR sequence to accurately identify focal myocardial fibrosis [1,2]. In nonischemic dilated cardiomyopathy (DCM), fibrosis is present in only approximately 30–40% of cases and shows a “midwall” pattern, being mostly located in the interventricular septum [1]. In hypertrophic cardiomyopathy (HCM), LGE can be observed in any location or in any distribution pattern, although it is most frequently detected in the ventricular septum [3]. Severe myocardial fibrosis, detected by LGE-MRI, has a strong prognostic value for both DCM and HCM patients [4,5]. However, LGE-MRI can only delineate focal myocardial fibrosis but not diffuse interstitial fibrosis. Non-invasive assessment of diffuse

interstitial fibrosis is therefore important for better risk stratification of NIC patients.

Myocardial native T1 mapping emerged as a non-invasive method to quantify diffuse myocardial abnormalities. Extracellular volume (ECV), calculated by pre- and post-T1 mapping, can detect diffuse myocardial abnormalities in various myocardial diseases, including diastolic heart failure [6], diabetic cardiomyopathy [7], and cardiac amyloidosis [8]. Recent studies have shown that native (non-contrast) T1 mapping can differentiate the HCM myocardium from a healthy myocardium [9]. This evidence supports the clinical importance of the T1 mapping technique for the management of myocardial diseases; however, meta-analytical data regarding the ability of T1 mapping to differentiate between healthy controls (HCs) and NIC patients are limited. In this systematic review and meta-analysis, we sought to compare the values of native T1 and ECV between NIC patients and healthy subjects.

2. Materials and methods

2.1. Literature search

Using an electronic search, we systematically searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and the Web of Science Core Collection. Search terms are presented as supplementary data (Supplementary Text 1). References from published reviews and those of original studies were verified manually. Two investigators (SM and KM) independently screened candidate articles by examining the title and abstract after uploading the list of citations into the Endnote X7 software (Thomson Reuters, Philadelphia, PA, USA). Subsequently, articles still regarded as candidates by at least one investigator were independently scrutinized through full-text reading. Duplicate use of the same data was carefully evaluated. A decision regarding final inclusion was made after resolving discrepancies between the two investigators. The study protocol has been registered in the international prospective register of systematic reviews (PROSPERO) [10] under registration number 42017065847.

2.2. Eligibility criteria

Studies were included if they met the following criteria: (1) a cohort, case-control, or cross-sectional design; (2) the values of T1 mapping were provided for both HCs and NIC patients; and (3) NIC patients met the accepted diagnostic criteria for DCM or HCM. Diagnoses of DCM and HCM were based on the judgement by the authors of original research. Patients with myocardial infiltration due to amyloidosis, iron accumulation, lipid storage disease, or myocardial inflammation were excluded. Modified Look-Locker inversion recovery (MOLLI) T1 mapping from 1.5- and 3.0-T MRI scanners was included. Shortened MOLLI was allowed. Simultaneously reported results from two or more modes of T1 mapping were evaluated separately. Non-English published reports and conference abstracts were allowed. Studies covering only sensitivity or specificity were not included.

2.3. Outcomes and statistics

Co-primary outcomes were myocardial T1 and ECV values for DCM and HCM in comparison to HC. Weighted mean differences (MDs) with 95% confidence intervals (CIs) were calculated for native T1 and ECV values. If T1 mapping parameters of septal and non-septal segments were reported simultaneously, septal myocardial data were chosen for all analyses. Similarly, if these parameters were measured in the basal, mid, and apical regions, data at the mid-ventricular level were chosen. Results of eligible studies obtained using 1.5-T and 3.0-T MRI scanners are shown separately.

2.4. Risk of bias

The quality of original studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS) criteria [11]. MINORS contains 12 items, and the quality of studies was scored from 0 to 24. All discrepancies were resolved through discussion. Publication bias was assessed using plots of study results against precision of the study (funnel plots).

2.5. Data synthesis

Results of T1 mapping are expressed as the mean \pm standard deviation (SD). Means and SDs were also calculated for studies that reported the median with the interquartile range. Data were independently crosschecked after extraction by two investigators. We computed effect sizes (expressed as Cohen's *d*). Effect sizes between 0.2 and 0.5 were considered small, those between 0.5 and 0.8 were considered moderate, and those more than 0.8 were considered large. Pooled analyses were performed using the generic inverse variance method with a random effects model. Heterogeneity was indicated by I^2 , wherein 0% meant no heterogeneity and 100% meant the strongest heterogeneity. The Review Manager version 5.3 software (Cochrane, London, UK) was used to draw paired forest plots.

3. Results

3.1. Literature search and study characteristics

Of 1983 candidate articles, we finally selected 16 eligible reports [9,12–26]. Three of the studies presented two cohorts, and therefore, we included 19 independent cohorts (Fig. 1). Among the 16 included reports, six were from the UK, three from Germany, two from China, one each from the Netherlands, Australia, Korea, and Poland, and one was an international collaboration. The publication dates ranged from 2012 to 2018 (Table 1). One was an abstract in English [26], and the others were full-length articles in English [9,12–25]. Non-English published reports were not identified. A total of 264 DCM patients, 319 HCM patients, and 485 HCs were included in our analysis (Table 1). The final diagnoses of DCM and HCM were made based on a combination of symptoms, laboratory test results, a family history, genetic testing, pathology, and imaging criteria by the authors of the eligible studies. The MINORS scores ranged from 10 to 22, with an average of 16.7 (Supplementary Table 1). Among the 19 cohorts, native T1 mapping was performed in 17 cohorts, and ECV was measured in 12 cohorts. DCM and HCM were evaluated in 9 and 10 cohorts, respectively. MRI systems using 1.5-T and 3.0-T were used in 10 and 9 cohorts, respectively (Table 1). Visual inspection of the funnel plots (Supplementary Fig. 1) indicated a possible publication bias.

3.2. Meta-analysis of native T1 mapping

Native T1 values were measured in four cohorts involving 74 DCM patients and 141 HCs using a 1.5-T scanner (Table 2). The mean (\pm SD) native T1 values in the DCM patients and HCs were 1021 ± 58 and 979 ± 50 ms (Cohen's *d* = 0.79), respectively. The meta-analysis showed that native T1 was significantly longer in the patients with DCM than in HCs (MD = 45.26, 95% CI: 30.92–59.59, $I^2 = 19\%$, $p < 0.001$) (Fig. 2). Similarly, native T1 values were measured in four cohorts involving 105 HCM patients and 141 HCs using a 1.5-T machine (Table 2). The mean native T1 values in the HCM patients and HCs were 1019 ± 60 and 963 ± 41 ms (Cohen's *d* = 1.12), respectively. The meta-analysis showed that native T1 was significantly longer in the HCM patients than in HCs (MD = 47.09, 95% CI: 32.42–61.76, $I^2 = 27\%$, $p < 0.001$) (Fig. 2). At 3.0-T, native T1 values were measured in five cohorts involving 190 DCM patients and 156 HCs and in three cohorts involving 186 HCM patients and 79 HCs (Table 2). The mean

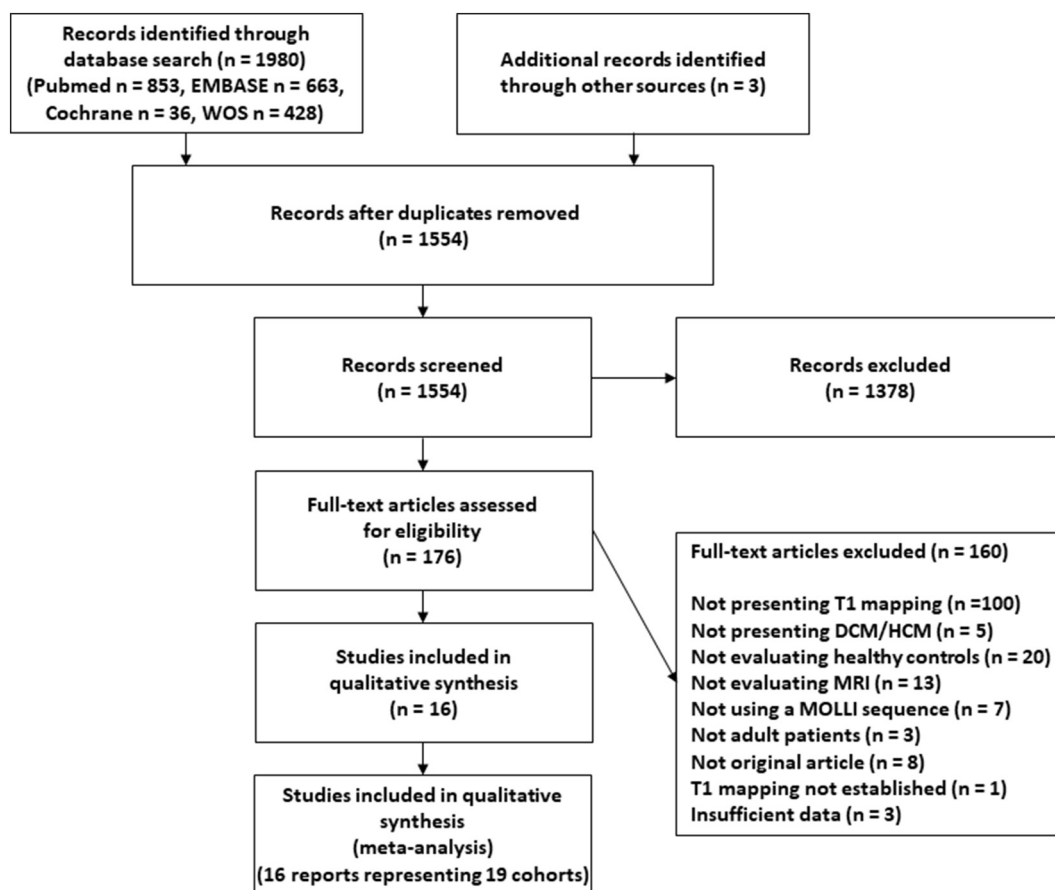


Fig. 1. PRISMA flow diagram.

native T1 values were 1193 ± 67 ms in the DCM patients and 1103 ± 61 ms in HCs (Cohen's $d = 1.40$), whereas these values were 1201 ± 61 ms in the HCM patients and 1087 ± 60 ms in HCs (Cohen's $d = 1.88$). The meta-analysis showed that native T1 was significantly longer in both DCM and HCM patients than in HCs (DCM: MD = 82.52, 95% CI: 47.60–117.44, $I^2 = 93\%$, $p < 0.001$; HCM: MD = 115.87, 95% CI: 50.71–181.04, $I^2 = 98\%$, $p < 0.001$) (Fig. 3). The native T1 values showed considerable heterogeneity at 3.0-T.

3.3. Meta-analysis of ECV

ECV measurements were performed in three cohorts involving 57 DCM patients and 87 HCs at 1.5-T (Table 2). The mean ECVs were $29 \pm 4\%$ and $24 \pm 3\%$ in the DCM patients and HCs (Cohen's $d = 1.46$), respectively. The meta-analysis showed that ECV was significantly higher in the DCM patients than in HCs (MD = 4.26, 95% CI: 3.06–5.46, $I^2 = 0\%$, $p < 0.001$) (Fig. 4). In contrast, ECV measurements in HCM patients at 1.5-T were only reported in a small number of cohorts, involving 28 HCM patients and 64 HCs (Table 2). The mean ECVs were $28 \pm 4\%$ and $27 \pm 3\%$ in the HCM patients and HCs (Cohen's $d = 0.30$), respectively. The pooled MD of these cohorts was 1.49 (95% CI: -1.45 – 4.43 , $I^2 = 80\%$, $p = 0.32$) (Fig. 4). At 3.0-T, ECVs were measured in four cohorts involving 172 DCM patients and 144 HCs and in three cohorts involving 158 HCM patients and 67 HCs (Table 2). The mean ECV values were $36 \pm 9\%$ in the DCM patients and $26 \pm 7\%$ in HCs (Cohen's $d = 1.23$), whereas these values were $32 \pm 7\%$ in the HCM patients and $25 \pm 8\%$ in HCs (Cohen's $d = 0.96$). The meta-analysis showed that ECVs were significantly higher in both DCM and HCM patients than in HCs (DCM: MD = 8.40, 95% CI: 2.94–13.86, $I^2 = 95\%$, $p = 0.003$; HCM: MD = 8.02, 95% CI: 5.45–10.59, $I^2 = 56\%$, $p < 0.001$) (Fig. 5).

4. Discussion

The current systematic review and meta-analysis showed that native myocardial T1 values and ECVs were significantly increased in patients with HCM and DCM compared with those in HCs, irrespective of the magnetic field strength of the MRI scanner. Assessment of native T1 values and ECVs may be useful to detect and quantify diffuse interstitial myocardial fibrosis missed by the LGE-MRI sequence.

HCM is the most common genetic cardiomyopathy and the cause of sudden cardiac death (SCD) in young individuals. Hypertrophied myocytes are arranged chaotically, with increased extracellular matrix accumulation. The myocardium may also contain ischemic areas, caused by the obstruction of the microvasculature, with replacement fibrosis and scar tissue. This modified myocardial structure is associated with the occurrence of malignant ventricular arrhythmia, such as ventricular tachycardia and fibrillation. Accurate evaluation of myocardial fibrosis is thus important for risk stratification of HCM patients. Chan et al. [5] studied the prognostic utility of LGE-MRI in 1293 HCM patients and demonstrated that $LGE \geq 15\%$ of the left ventricular mass was associated with a twofold increase in the risk of an SCD event in these patients, otherwise considered to be at a lower risk. Although severe fibrosis, detected by LGE-MRI, is a strong prognostic marker in HCM patients, diffuse interstitial fibrosis cannot be assessed by LGE-MRI because the enhanced area is defined based on the difference in the signal intensity relative to that of the normal myocardium; if there is diffuse fibrosis, no difference in signal intensity will be observed. To overcome this limitation, T1 mapping techniques have been developed, which allow quantification of the relaxation time of the myocardium. The native T1 value is prolonged in HCM and correlates with the wall thickness, suggesting that the former is a marker of the disease severity [9]. ECV can be used in the differential diagnosis of HCM vs. athletic remodeling in the hearts

Table 1
Characteristics of 19 cohorts.

Cohort	Country	MRI machine	MRI sequence	MRI parameters	Patients (n)	Controls (n)	Native T1 time (ms), patients	Native T1 time (ms), controls	ECV (%), patients	ECV (%), controls	Clinical diagnosis
aus dem Siepe 2015 (DCM)	Germany	1.5-T	MOLLI	Native T1, ECV	29	56	1056 ± 62	1020 ± 40	27 ± 4	23 ± 3	DCM defined according to ESC criteria
Brouwer 2014 (HCM)	Netherlands	1.5-T	MOLLI	ECV	16	14	NA	NA	26 ± 3	26 ± 2	HCM defined based on clinical features
Costello 2017 (DCM)	Australia	3.0-T	ShMOLLI	Native T1, ECV	22	57	1191 ± 52	1125 ± 45	27 ± 3	25 ± 3	DCM defined based on clinical features
Dass 2012 (DCM)	UK	3.0-T	ShMOLLI	Native T1	18	12	1225 ± 42	1178 ± 13	NA	NA	DCM defined based on clinical features
Dass 2012 (HCM)	UK	3.0-T	ShMOLLI	Native T1	28	12	1209 ± 28	1178 ± 13	NA	NA	HCM defined based on gene mutations and clinical features
Fontana 2012 (HCM)	UK	1.5-T	ShMOLLI	ECV	12	50	NA	NA	30 ± 3	27 ± 3	HCM defined based on clinical features
Fontana 2014 (HCM)	UK	1.5-T	ShMOLLI	Native T1	46	52	1026 ± 64	967 ± 34	NA	NA	HCM defined according to ESC criteria
Goebel 2016 (DCM)	Germany	1.5-T	MOLLI	Native T1	17	54	992 ± 37	955 ± 34	NA	NA	DCM defined according to ESC criteria
Goebel 2016 (HCM)	Germany	1.5-T	MOLLI	Native T1	12	54	980 ± 44	955 ± 34	NA	NA	HCM defined according to ESC criteria
Hinojar 2015 (HCM)	International	3.0-T	MOLLI	Native T1, ECV	95	23	1169 ± 41	1044 ± 18	31 ± 6	24 ± 6	HCM defined according to ESC criteria
Hong 2015 (DCM)	Korea	3.0-T	MOLLI	Native T1, ECV	41	10	1248 ± 67	1205 ± 37	32 ± 6	26 ± 2	DCM defined based on clinical features
Kampf 2018 (DCM)	Germany	1.5-T	MOLLI	Native T1, ECV	12	10	984 ± 49	937 ± 58	30 ± 4	26 ± 2	Definition of DCM not presented
Malek 2015 (HCM)	Poland	1.5-T	ShMOLLI	Native T1	25	20	989 ± 49	940 ± 45	NA	NA	HCM defined according to ESC criteria
Mordi 2016 (DCM)	UK	1.5-T	MOLLI	Native T1, ECV	16	21	1017 ± 42	952 ± 31	31 ± 4	26 ± 3	DCM defined based on clinical features
Puntmann 2013 (DCM)	UK	3.0-T	MOLLI	Native T1, ECV	27	30	1239 ± 57	1070 ± 55	41 ± 10	27 ± 10	DCM defined according to ESC criteria
Puntmann 2013 (HCM)	UK	3.0-T	MOLLI	Native T1, ECV	25	30	1254 ± 43	1070 ± 55	40 ± 10	27 ± 10	HCM defined according to ESC criteria
Puntmann 2014 (DCM)	UK	3.0-T	MOLLI	Native T1, ECV	82	47	1145 ± 37	1055 ± 22	40 ± 9	27 ± 9	DCM defined according to ESC criteria
Wu 2016 (HCM)	China	3.0-T	MOLLI	Native T1, ECV	38	14	1241 ± 79	1115 ± 38	31 ± 3	24 ± 3	HCM defined based on clinical features
Yin 2014 (HCM)	China	1.5-T	MOLLI	Native T1	22	15	1061 ± 36	1010 ± 45	NA	NA	Definition of DCM not presented

If a report contained both dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) data, we treated the datasets as two independent cohorts. Continuous data were extracted as the mean ± standard deviation.

MOLLI = modified Look-Locker inversion recovery; ShMOLLI = shortened MOLLI; ECV = extracellular volume; ESC = European Society of Cardiology; NA = data not available.

of athletes [27]. In our study, native T1 values and ECVs were significantly elevated in HCM patients compared with those in HCs, both in 1.5- and 3.0-T magnetic fields, indicating a robust capability of the T1 mapping technique to differentiate between a diseased myocardium in HCM patients and the normal myocardium. In DCM, prior studies have demonstrated that LGE is a powerful predictor of ventricular arrhythmia events in both ischemic cardiomyopathy and NIC patients

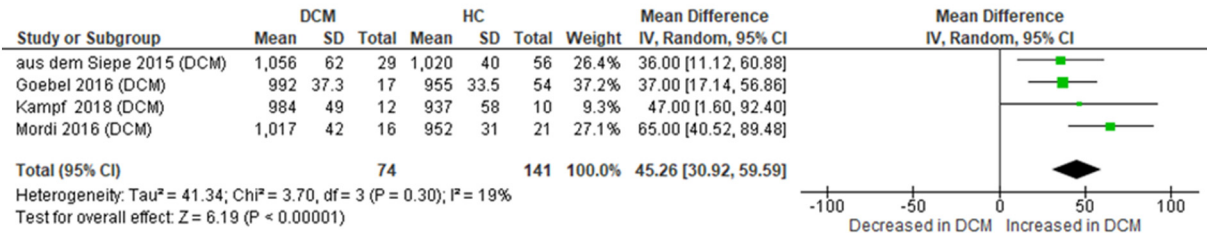
[28,29]. LGE typically occurs in a midwall pattern, but in the majority (~70%) of DCM patients, there is a lack of any detectable LGE. T1 mapping has been proposed as a method to detect diffuse interstitial fibrosis missed by LGE in DCM patients. ECV values reflect the myocardial collagen content in DCM and may serve as a non-invasive imaging biomarker to monitor the therapy response and aid in the risk stratification of different stages of DCM [12]. In our study, native T1 values and ECVs were

Table 2
Summary of results.

Random effect model	Cohort number	Patients (n)	Controls (n)	MD (95% CI)	p	I ²
Native T1 at 1.5-T						
DCM	4	74	141	45.26 (30.92–59.59)	<0.001	19%
HCM	4	105	141	47.09 (32.42–61.76)	<0.001	27%
Native T1 at 3.0-T						
DCM	5	190	156	82.52 (47.60–117.44)	<0.001	93%
HCM	4	186	79	115.87 (50.71–181.04)	<0.001	98%
ECV at 1.5-T						
DCM	3	57	87	4.26 (3.06–5.46)	<0.001	0%
HCM	2	28	64	1.49 (–1.45–4.43)	0.32	80%
ECV at 3.0-T						
DCM	4	172	144	8.40 (2.94–13.86)	0.003	95%
HCM	3	158	67	8.02 (5.45–10.59)	<0.001	56%

DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ECV = extracellular volume. I² = 0%, no heterogeneity; 0% < I² < 30%, low heterogeneity; 30% ≤ I² < 50%, moderate heterogeneity; 50% ≤ I² < 75%, substantial heterogeneity; and I² ≥ 75%, considerable heterogeneity.

DCM



HCM

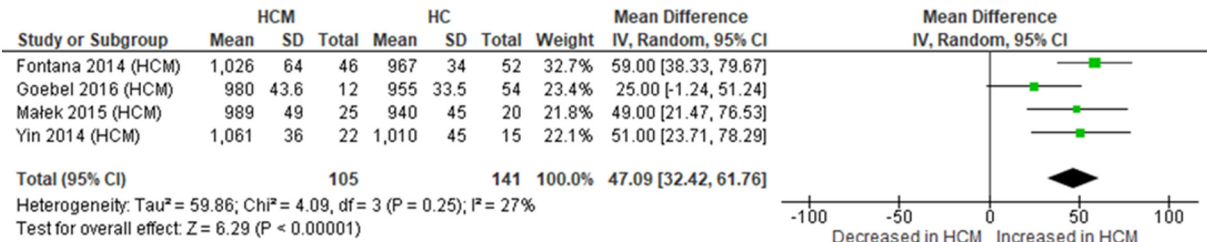


Fig. 2. Forest plots of mean differences in native T1 between non-ischemic cardiomyopathy patients and healthy controls at 1.5-T (DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; MD = mean difference; IV = inverse variance; CI = confidence interval).

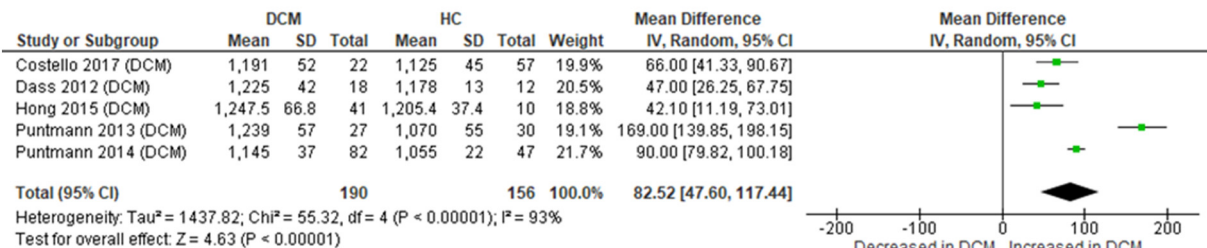
significantly elevated in DCM patients compared with those in HCs in both 1.5- and 3.0-T magnetic fields, indicating a robust capability of the T1 mapping technique to differentiate between a diseased myocardium in DCM patients and the normal myocardium. A further study is necessary to clarify whether abnormal findings on T1 mapping have an incremental prognostic value over LGE-MRI in patients with DCM.

A meta-analysis of native T1 value ranges in patients with NIC, compared with those in HCs, has recently been reported [30]. However, this review only included a limited number of studies on T1 mapping parameters, retrieved by searching PubMed and EMBASE. Searching one or two databases is insufficient for a meta-analysis of observational

studies [31]. We used PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and the Web of Science Core Collection. Importantly, we conclusively analyzed not only native T1 but also ECV data. A pooled analysis of ECV from two studies, which compared HCM patients and HCs at 1.5-T, found no significant differences, which might have been due to a limited number of cohorts.

This meta-analysis has several limitations. Thus, the number of qualified papers was small. As noted above, there were only two cohorts, in which the ability of ECV to diagnose HCM was evaluated at 1.5-T. Statistical heterogeneity of the results of native T1 and ECV measurements was high at 3.0-T. Despite the recognized potential of T1 mapping for clinical use, the methods and protocols have yet to be fully standardized.

DCM



HCM

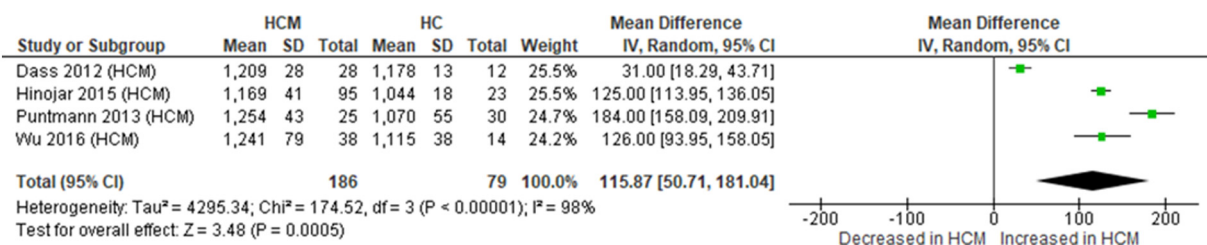
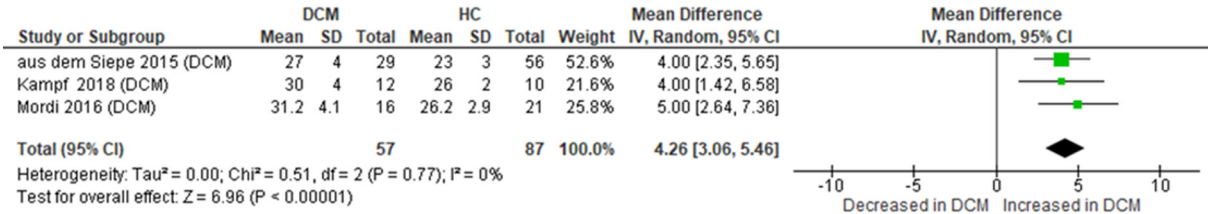


Fig. 3. Forest plots of mean differences in native T1 between non-ischemic cardiomyopathy patients and healthy controls at 3.0-T (DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; MD = mean difference; IV = inverse variance; CI = confidence interval).

DCM



HCM

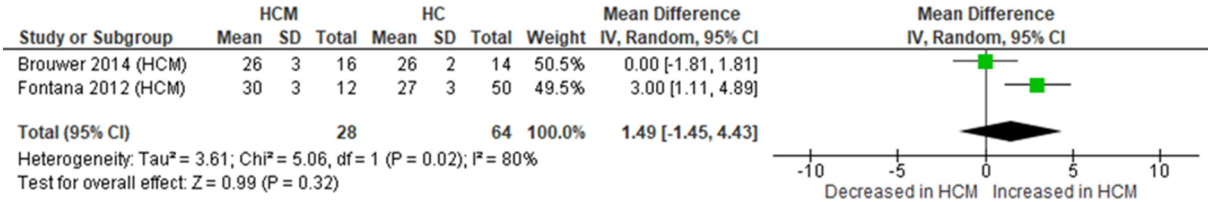


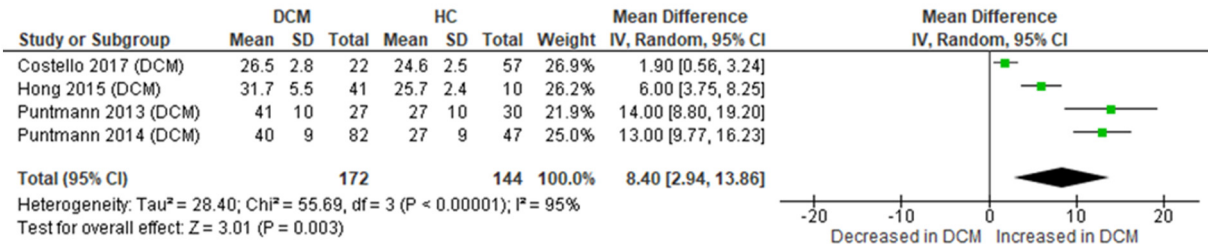
Fig. 4. Forest plots of mean differences in ECV between non-ischemic cardiomyopathy patients and healthy controls at 1.5-T (DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; MD = mean difference; IV = inverse variance; CI = confidence interval).

We included only the MOLLI sequence and performed separate analyses at 1.5-T and 3.0-T. However, different settings for T1 mapping might have resulted in the heterogeneity. Furthermore, we were unable to compare NIC patients with age- and sex-matched HCs because of the lack of data. As LGE is a marker of much denser replacement fibrosis and a very different tissue substrate, we carried out subgroup analysis based on segments with and without LGE when a sufficient number of cohorts was available, which was only possible for native T1 mapping using a 3.0-T machine. There were no significant differences in native T1 values between LGE-positive and LGE-negative groups. However, this subgroup analysis might have been inaccurate because of a limited number of cohorts.

5. Conclusions

This systematic review and meta-analysis demonstrated that both native T1 and ECV values could be useful as surrogate markers for the detection of diffuse myocardial fibrosis in NIC patients. These results suggest a specific advantage of T1 mapping, which enables non-invasive assessment of important myocardial tissue characteristics. However, one should be aware that T1 mapping only allows the detection of abnormalities in the myocardium but does not diagnose a specific disease. Although the values may be raised in DCM and HCM, T1 mapping cannot differentiate between the two conditions. These issues have to be considered when clinically applying T1 mapping techniques.

DCM



HCM

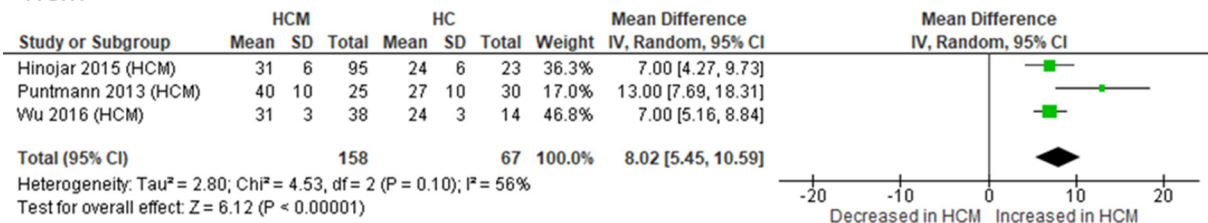


Fig. 5. Forest plots of mean differences in ECV between non-ischemic cardiomyopathy patients and healthy controls at 3.0-T (DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; MD = mean difference; IV = inverse variance; CI = confidence interval).

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2019.100422>.

Author contributions

The author contributions were as follows: conception and design (SM, SK, KM, NH, KA, HW, TI, KM, KK, and KT); data analysis and interpretation (SM, SK, KM, and NH); draft preparation (SM, SK, KM, and NH); and revision of the manuscript (KA, HW, TI, KM, KK, and KT). All authors have approved the final article.

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Declaration of competing interest

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