European Journal of Preventive Cardiology

ESC European Society of Cardiology

Research letter

European Journal of Preventive Cardiology
0(00) 1–4

DOI: 10.1177/2047487319874352
journals.sagepub.com/home/cpr

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The prognostic value of late gadolinium enhancement in hypertrophic cardiomyopathy: An updated meta-analysis

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Hypertrophic cardiomyopathy (HCM) is a genetic-based cardiomyopathy and its prevalence ranges from 0.02 to 0.23% in adults.[1] As it is the most common cause of sudden cardiac death (SCD) in the young,[2] different risk scores have been proposed to properly identify patients that would benefit from a primary prevention with an implantable cardioverter-defibrillator (ICD). European Society of Cardiology (ESC) guidelines suggest using the HCM Risk-SCD Calculator that incorporates age, extent of left ventricular hypertrophy, left atrial size, left ventricular outflow gradient, family history of SCD, non-sustained ventricular tachycardia, and unexplained syncope to predict five-year SCD risk.[1] These guidelines mention the potential utility of cardiac magnetic resonance (CMR) mainly in the case of poor echo windows, while the American College of Cardiology/American Heart Association guidelines recognize the possible value of late gadolinium enhancement (LGE) for SCD risk stratification, but they do not include it among the major risk factors.[2] The aim of the present study-level meta-analysis was to explore the prognostic value of LGE at CMR for adverse fatal events. The protocol of this study was registered on PROSPERO (registration number: CRD42019136013).

Electronic databases were searched for studies that investigated the prognostic value of LGE in patients with HCM. The process was performed according to the PRISMA statement.[3] Two authors extracted data on patient characteristics and outcomes. The outcomes of interest were SCD or aborted SCD, all-cause mortality, and cardiovascular (CV) mortality. Random-effects odds ratios (ORs) were estimated using a DerSimonian–Laird method with a person–year approach. Heterogeneity was calculated using the I^2 test and publication bias was visually assessed with funnel plots. To better characterize the prognostic value of the presence of LGE for the outcomes of interest, we also calculated summary sensitivity, specificity, likelihood ratios, diagnostic ORs, and summary receiver-operating characteristic (SROC) curves. The quality of the studies was assessed using a score specifically developed for prognostic studies.[4] Univariate meta-regression for unadjusted log-OR was performed to explore the potential moderator effect of mean age, LGE % of left ventricle (LV), gender (expressed as male percentage), and the available factors included in the HCM Risk-SCD Calculator[1] (expressed as percentage for dichotomous variables and as mean for continuous ones). Statistical analyses were conducted using Review Manager version 5.3, OpenMeta-Analyst, and MetaDTA.

Seven studies met our inclusion criteria and were included in the analyses ($n = 3351$; mean follow-up 2.97 ± 0.63 years; Table 1 and Supplementary Figure 1S). A total of 57% of the patients had LGE at CMR, and the mean LGE % of LV was 6.98 ± 2.9. The mean annualized incidence of SCD/aborted SCD in patients with LGE was $1.6\% \pm 0.7\%$ versus

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0.2% ± 0.2% in patients without LGE. The presence of LGE was associated with an increased incidence of SCD or aborted SCD (OR = 3.34; 95% CI, 1.97–5.69; $p < 0.001$; Figure 1(a)), all-cause mortality (OR = 1.82; 95% CI, 1.24–2.67; $p = 0.002$; Figure 1(b)), and CV mortality (OR = 3.03; 95% CI, 1.69–5.40; $p < 0.001$; Figure 1(c)) compared with the absence of LGE at CMR. As shown by the SROC curves (Figure 1(a)–(c)), the presence of LGE showed a sensitivity of 89% (95% CI, 77–95%) and a specificity of 39% (95% CI, 31–47%) in predicting SCD/aborted SCD and similar values in predicting all-cause and CV mortality. Moreover, the absence of LGE had a negative predictive value of 98.9% (95% CI, 98.3–99.3%) for SCD/aborted SCD. No publication bias was detected and univariate meta-regression analysis did not show any moderator effect of the variables considered on the outcomes of interest. All studies were considered well designed and conducted, with the exception of one study[5] (Supplementary Table 1S); however, the results remained consistent after its exclusion at sensitivity analysis.

We must acknowledge some limitations. First, it is a study-level meta-analysis; therefore, it was not possible to properly investigate the influence of all the possible confounders on the outcomes of interest. To overcome this limitation, we performed a meta-regression analysis; nevertheless, the absence of any moderator effect may be due to a type-two error related to the limited number of studies included in the analyses.

Our study is the most updated on the topic and extends and confirms the results of previous works,[6] overcoming some of their limitations as the inclusion of studies with overlapping subjects.[7] It demonstrates that the presence of LGE at CMR in patients with HCM has a substantial prognostic value for fatal events and, in particular, for SCD. Therefore, LGE assessment should be considered, especially in borderline cases according the ESC HCM Risk-SCD Calculator, to improve the identification of HCM patients who could benefit from ICD implantation in primary prevention and also to intensify medical therapy and/or follow-up, even at a young age.

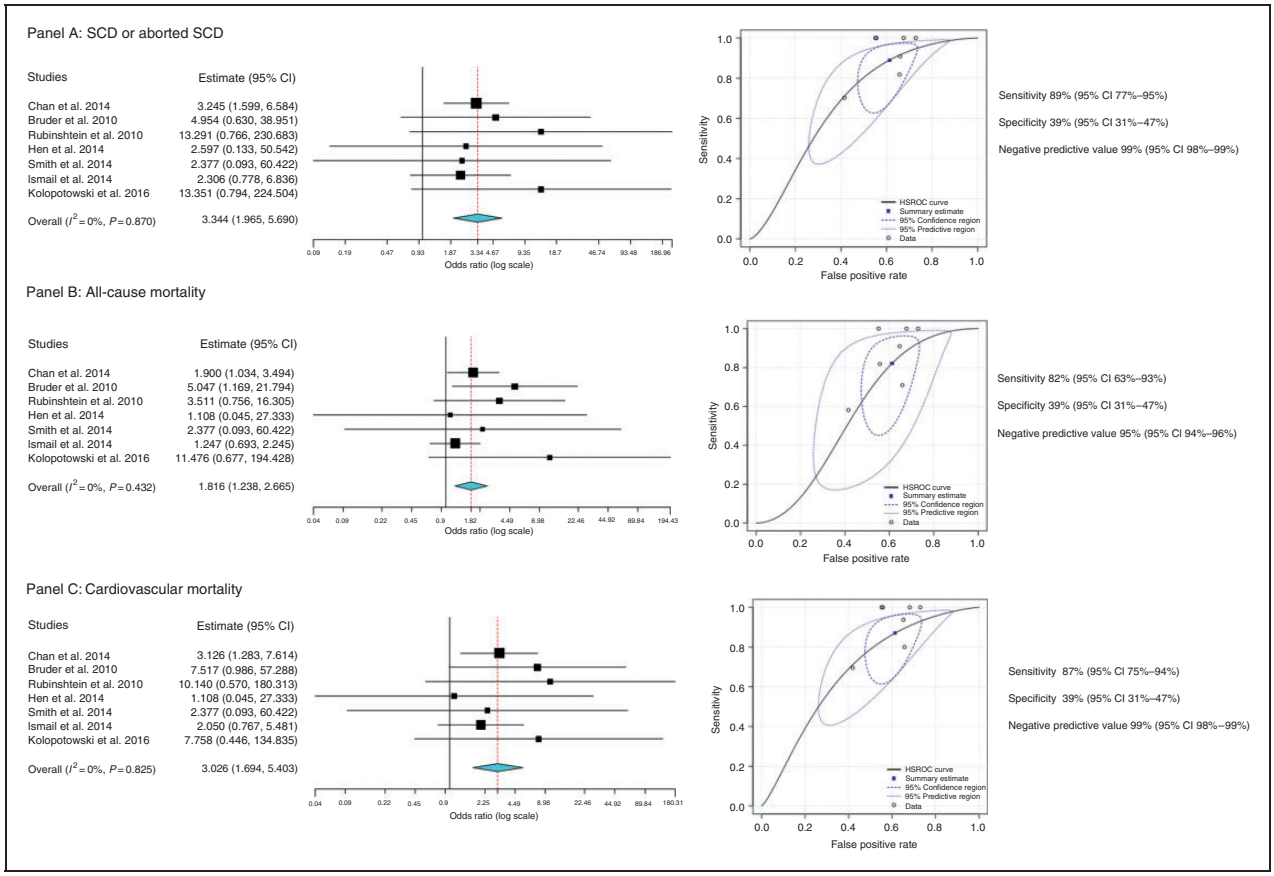

Figure 1. Prognostic value of late gadolinium enhancement: adverse event incidence in patients with LGE versus without LGE. HSROC: hierarchical summary receiver-operating characteristic; LGE: late gadolinium enhancement; SCD: sudden cardiac death.

Table 1. Study characteristics.

	Brunder et al. (2010)[8]	Chan et al. (2014)[9]	Hen et al, (2014)[10]	Ismail et al. (2014)[11]	Klopotowski et al. (2016)[12]	Rubinshtein et al. (2010)[13]	Smith et al. (2014)[5]
Inclusion criteria	Pt with known or suspected HCM who underwent CMR	Pt with HCM who underwent CMR	Pt with HCM who underwent CMR	Consecutive pt with HCM referred for CMR	Consecutive pt with HCM referred for CMR	Pt with HCM who underwent ce-MRI	All pt aged $\leq$21 years referred for CMR
Exclusion criteria	CAD, aortic stenosis, amyloidosis, hypertension, septal ablation or myectomy	MRI incompatible device, history of sustained VT/VF, claustrophobia, CAD, other myocardial diseases, septal myectomy or alcohol ablation	CAD, congenital heart disease, severe valvular disease, septal myectomy or alcohol ablation	CAD, septal myectomy or alcohol ablation, contraindication to ce-CMR	CAD, septal myectomy or alcohol ablation, myocarditis, Fabry disease and Noonan syndrome, contraindication to ce-MRI	MRI incompatible device, septal myectomy or ablation; MRI performed without contrast agent	Congenital heart disease or an underlying syndrome or storage condition predisposing to secondary HCM
No. of patients enrolled (% of patients with LGE)	220 (67.2)	1293 (42.4)	345 (73.0)	711 (66.2)	328 (68.9)	424 (56.4)	30 (56.7)
Study design	Prospective bicentric cohort study	Prospective multicentric cohort study	Retrospective monocentric cohort study	Prospective monocentric cohort study	Prospective monocentric cohort study	Retrospective monocentric cohort study	Retrospective monocentric study
Aims of the study	To demonstrate that the presence of scar visualized by CMR predicts future cardiac death in HCM	To investigate the prognostic value of LGE in HCM	To analyze the usefulness of LGE in predicting cardiovascular events in HCM	To determine the independent prognostic significance of myocardial fibrosis in HCM	To elucidate the prognostic value of LGE along with full standard SCD risk assessment in HCM	To explore the association of LGE with genetic testing, symptoms, VT/VF, or SCD in HCM	To characterize the association of LGE with clinical outcomes in pediatric HCM
Follow-up (months)	36.3	39.6	21.8	42	37	43	26.9
Mean age (years)	58	46	59	56.3	45	55	14.1
Male (%)	61.4	63	62	70	58.5	59	56.7
LGE (% of LVM)	3.2	9	NA	9.5	NA	6.2	NA
% of pt with maximal wall thickness >30 mm	3.6	5	7.8	4.5	10.4	NA	NA
History of non-sustained VT (%)	NA	20	NA	5.4	36.6	19.1	NA
Family history of SCD (%)	4.5	17	10.7	10.8	20.7	6	NA
Unexplained syncope (%)	5.5	9	12.8	10	12.8	16	NA
LVOT obstruction >30 mmHg (%)	10.9	23	NA	29.3	33.8	NA	26.7

CAD: coronary artery disease; ce: contrast enhanced; CMR: cardiac magnetic resonance; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; LVM: left ventricular mass; LVOT: left ventricular outflow tract; NA: not available; pt: patients; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

Author contributions

FF and RA performed the literature search, assessed the selected articles, and collected the data of interest. FA and FF performed the statistical analyses and drafted the manuscript. All authors were involved in the conception and design of the study and interpretation of the data, revised the manuscript critically for important intellectual content, and finally approved the submitted manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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