BACKGROUND: Patients with acute myocarditis (AM) are at increased risk of adverse cardiac events after the index episode. Late gadolinium enhancement (LGE) detected by cardiovascular magnetic resonance in patients with AM plays an important diagnostic role, but its prognostic significance remains unresolved. This systematic review and meta-analysis sought to assess the prognostic implications of cardiovascular magnetic resonance-derived LGE in patients with AM.

METHODS: Data search was conducted from inception through February 28, 2020, using the following Medical Subject Heading terms: Myocarditis, CMR, Magnetic Resonance Imaging, Magnetic Resonance. From 2422 articles retrieved, we selected 11 studies reporting baseline cardiovascular magnetic resonance assessment and long-term clinical follow-up in patients with AM. Hazard ratios and CIs for a combined clinical endpoint were recorded for LGE presence, extent (>2 segments or >10% of left ventricular [LV] mass or >17g) and location (anteroseptal versus non-anteroseptal). A combined endpoint comprised all-cause mortality, cardiac mortality, and major adverse cardiovascular events. Hartung and Knapp correction improved robustness of the results. Prespecified sensitivity analyses explored potential sources of heterogeneity. The meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines.

RESULTS: LGE presence (pooled hazard ratios, 3.28 [95% CIs, 1.69–6.39], P<0.001 [95% CIs, 1.33–8.11] after Hartung and Knapp correction) and anteroseptal LGE (pooled-hazard ratios, 2.58 [95% CIs, 1.87–3.55], P<0.001 [95% CIs, 1.64–4.06] after Hartung and Knapp correction) were associated with an increased risk of the combined endpoint. Extensive LGE was associated with worse outcomes (pooled-hazard ratios, 1.96 [95% CIs, 1.08–3.56], P=0.027), but this association was not confirmed after Hartung and Knapp correction (95% CIs, 0.843–4.57).

CONCLUSIONS: LGE presence and anteroseptal location at baseline cardiovascular magnetic resonance are important independent prognostic markers that herald an increased risk of adverse cardiac outcomes in patients with AM.

REGISTRATION: https://www.crd.york.ac.uk/PROSPERO/ Unique identifier: CRD42019146619.
Acute myocarditis (AM) is an inflammatory disease of the myocardium with a heterogeneous cause and natural history. While the majority of patients seem to have a benign clinical course, however, most patients are now being diagnosed noninvasively with cardiovascular magnetic resonance. In addition to being of diagnostic importance, there is growing evidence that the presence, extent, and regional location of LGE assume prognostic significance. However, due to the low incidence of the condition and relatively low event rates, observational studies addressing this have been limited by small sample sizes, short follow-up durations, and the use of broad composite end points. We therefore undertook a systematic review and meta-analysis of the available literature. To account for the small number of studies available, the Hartung and Knapp correction was used to improve the robustness of CI estimates. Based on data from 2328 patients derived from 11 independent cohorts, we showed that the presence of LGE conferred a significant adjusted 3-fold increased risk of the combined end point of all-cause mortality and major adverse cardiac events. Anteroseptal location but not LGE extent was also associated with the clinical outcome when the stringent Hartung and Knapp correction was applied. Our meta-analysis demonstrates that the presence and location of LGE may identify a subgroup of patients with acute myocarditis who warrant more intensive clinical surveillance for adverse cardiac events.

**CLINICAL PERSPECTIVE**

Acute myocarditis is an inflammatory myocardial disease, which can be complicated by adverse cardiac events, including sudden cardiac death and heart failure. Hitherto, endomyocardial biopsy has been the cornerstone of diagnosis; however, most patients are now being diagnosed noninvasively with cardiovascular magnetic resonance. The latter may reveal areas of late gadolinium enhancement (LGE) typically in an epicardial to mid-wall (nonischemic) distribution denoting tissue inflammation and early fibrosis. In addition to being of diagnostic importance, there is growing evidence that the presence, extent, and regional location of LGE assume prognostic significance. However, due to the low incidence of the condition and relatively low event rates, observational studies addressing this have been limited by small sample sizes, short follow-up durations, and the use of broad composite end points. We therefore undertook a systematic review and meta-analysis of the available literature. To account for the small number of studies available, the Hartung and Knapp correction was used to improve the robustness of CI estimates. Based on data from 2328 patients derived from 11 independent cohorts, we showed that the presence of LGE conferred a significant adjusted 3-fold increased risk of the combined end point of all-cause mortality and major adverse cardiac events. Anteroseptal location but not LGE extent was also associated with the clinical outcome when the stringent Hartung and Knapp correction was applied. Our meta-analysis demonstrates that the presence and location of LGE may identify a subgroup of patients with acute myocarditis who warrant more intensive clinical surveillance for adverse cardiac events.

**METHODS**

The authors declare that all supporting data are available within the article and its Data Supplement. As this was a systematic review and meta-analysis of aggregated data from existing published literature and did not recruit any new subjects, institutional review board approval or additional informed consent was not required.

**Systematic Review**

**Search Strategy**

We performed a systematic review of the English and non-English literature using PubMed, Cochrane Library, Medline, Embase, Web of Science, Cihahl, www.clinicaltrials.gov, and grey literature databases (OpenGrey and The Grey Literature Report by the New York Academy of medicine) from inception through February 28, 2020. Full-length publications in peer-reviewed journals or abstracts in international congresses that assessed the association of CMR-LGE and the risk of future clinical events in patients with clinically suspected or confirmed AM were retrieved. CMR variables of interest were the presence,12,13,16,19–21 extent,14–16,19,22 location,15–17,19,23 pattern,15,19 and distribution15,19 of LGE. The extent of LGE was evaluated either as left ventricular (LV) segments involved,15,16,22,24 grams,14 or as a percentage of LV mass.15,16,19 For LGE location, we searched for risk estimates for anteroseptal versus non-anteroseptal and inferolateral versus non-inferolateral location of LGE. For LGE pattern and distribution, we searched for mid-wall versus subepicardial, and patchy versus linear, respectively. Data sources were also identified through a manual search of the retrieved articles’ references. All abstracts from large international cardiovascular conventions were also sought and screened. Further details on the search strategy are provided in the Data Supplement.

**Study Eligibility**

Studies were deemed eligible if they analyzed data in patients with AM (interval time between symptom-onset and CMR ≤2...
weeks); and detailed LGE data (presence and/or location and/or extent); and evaluation of at least one of the following outcomes: all-cause or cardiac mortality and major adverse cardiovascular events (MACE). We defined the combined end point as the combination of any cause of death and MACE. The latter comprised of new heart failure, sustained ventricular tachycardia, aborted sudden cardiac death or appropriate implantable cardioverter defibrillator discharge, implantation of an cardioverter defibrillator or pacemaker, cardiac transplantation or ventricular assist device implantation, ventricular tachycardia ablation, or recurrence of myocarditis. Criteria used for study inclusion were estimates of the risk related to LGE presence, extent or location; survival models adjusted for confounders; otherwise, unadjusted (crude) estimates of the combined end point incidence were used. No restrictions were imposed with regard to the type AM diagnosis (clinical plus endomyocardial biopsy-based versus clinical plus CMR-based diagnosis), patient treatment (β-blockers and/or ACE [angiotensin-converting enzyme] inhibitor/angiotensin II receptor blocker versus medical monitoring), or study sample size. Studies with mean follow-up <9 months, in pediatric subjects (<18 years), or in patients affected by significant comorbidities or other cardiac diseases, were excluded. Comprehensive details of the included studies are provided in the Data Supplement.

Identification of Eligible Studies

The literature search, selection of studies, and extraction of data were performed by 2 independent authors (Drs Georgiopoulos and Figliozzi) who followed prespecified forms (see the Data Supplement). Where the required data were not available, we contacted the study authors.12,13,15,16 Disagreements were reviewed by a third investigator (Dr Masci) and finally resolved by consensus.

Meta-Analysis

The meta-analysis was conducted according to the framework of the Meta-analysis of Observational Studies in Epidemiology25 and registered in the PROSPERO database (CRD42019146619). Missing data were obtained from original study investigators whenever possible (see Data Supplement). No imputation methods were used.

Quality Assessment and Grading of Evidence

Two reviewers (Drs Georgiopoulos and Figliozzi) independently assessed the quality of the included studies using the validated Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control, cross-sectional, and cohort studies.26 Potential selection bias, comparability, and outcome assessment adequacy were evaluated. Quality assessment through the NOS indicated that 7 studies could be classified as good quality studies; 3 studies as fair quality studies; and 1 study as a poor-quality study. The criteria for converting NOS results (expressed as stars, Table I in the Data Supplement) to quality category were (1) good quality if NOS was ≥7 stars; (2) fair quality for studies with 5 to 6 stars; and (3) poor quality for studies ≤4 stars. The certainty of evidence for the association between LGE and the occurrence of adverse cardiac events in AM was evaluated by implementing The Grades of Recommendation, Assessment, Development and Evaluation Working Group system.27,28 In brief, we took into account the 5 Grades of Recommendation, Assessment, Development and Evaluation Working Group considerations (ie, risk of bias, consistency of effect, imprecision, indirectness, and publication bias) and adjudicated the certainty of the body of evidence separately for LGE presence, extent and location, and the incidence of the combined end point.

Data Extraction

Data were screened and extracted independently by 2 investigators (Drs Figliozzi and Georgiopoulos). We recorded hazard ratios (HRs) and corresponding 95% CIs as indices of effect size for (1) LGE presence; (2) LGE extent (ie, ≥2 involved myocardial segments or >10% of the total myocardial mass or >17g of LGE); (3) anteroseptal versus non-anteroseptal and inferolateral versus non-inferolateral location. We could not perform any analysis on the prognostic impact of LGE pattern and distribution since only 2 studies were eligible.15,19 When possible, multi-adjusted HRs were used (Table II in the Data Supplement).12,13,15,16,19,21,23 For 2 studies,15,16 additional data were obtained after contacting the authors. For 2 studies,12,13 95% CIs around the mean estimate were calculated as previously suggested.29 In one study,17 HR was calculated from the corresponding log-rank test as previously shown.30 For 2 studies,17,22 ORs and 95% CIs were calculated from available data as approximation of HRs in light of the small probability of the event of interest.31,32 For 1 study,16 a zero-cell correction was applied during OR calculation. One study was excluded from estimates of effect for the presence of LGE as study participants without LGE on CMR were excluded from the final study cohort.15

Data Synthesis and Analysis

We performed a meta-analysis of all eligible studies and obtained the pooled estimate separately for the association between LGE presence; extent; and LGE location and the combined end point comprising all-cause mortality, cardiac mortality, and MACE. We evaluated combined clinical end points since data for individual outcomes were available only in few eligible studies (Table III in the Data Supplement).

We evaluated heterogeneity using the I 2-statistic. Usually, when moderate to significant heterogeneity (P<0.1) exists among studies, a random-effects model is implemented.33 In our case, given that the power of such heterogeneity identification tests is low due to the small number of included studies, visual checks through forest plots were also performed to identify heterogeneity. Subsequently, to avoid false positive findings, we directly implemented a random-effects model. We utilized the inverse variance method with the Sidik-Jonkman 2-step heterogeneity estimator as a reference method, instead of the popular DerSimonian and Laird method, since the latter is known to underestimate heterogeneity in meta-analyses with a low number of individual studies.34 To tackle the small number of studies and provide more robust results, we applied the more conservative Hartung and Knapp (HK) correction to the overall estimate of CIs.35 The mean effect size and CIs of individual studies were illustrated with forest plots. We conducted prespecified sensitivity analyses where applicable to evaluate whether the estimates of the association of LGE findings on the combined end point differed within certain populations and to further explore potential sources of heterogeneity. Briefly, we excluded (1) studies with <50 participants;20-22; (2) studies of lower quality...
according to NOS evaluation\textsuperscript{12,13,19–23}; and/or studies with less likely AM (potential bias in AM diagnosis\textsuperscript{15} and delayed CMR\textsuperscript{19}). We did not implement the HK correction in sensitivity analyses since the number of studies was low (54) and the underlying distribution of the treatment effect with 3 or less df could substantially deviate from both the t- and the normal distribution, rendering the calculation of corrected 95% CIs problematic.\textsuperscript{36} In addition, random-effects meta-regression was performed to estimate the contribution of study moderators to the overall heterogeneity for the combined end point throughout the selected individual studies. Because of the small number of included studies, dedicated subgroup analysis was not performed.\textsuperscript{37}

The presence of publication bias was investigated graphically by funnel plots of precision and statistically by regression tests for asymmetry. The Egger test and the Begg and Mazumdar test were implemented. We also performed a linear regression of the intervention effect estimates on their standard errors weighting by 1/(variance of the intervention effect estimate). Statistical analysis was performed with STATA V12.1 (StataCorp, College Station, TX). The module admetan was used for meta-analysis in STATA. Two-tailed values of $P<0.05$ were deemed significant.

### RESULTS

#### Literature Search

The results of the literature search are depicted in Figure 1. We retrieved 2422 articles and after discarding duplicates (n=1051), the title and abstract of the remaining 1371 articles were screened and 1298 records were excluded. Full-text articles of the remaining 73 records were retrieved and examined. Ultimately, 62 studies were deemed not eligible (see Data Supplement) and the remaining 11 studies were selected for quantitative analysis.\textsuperscript{12–17,19–23}

#### Study Characteristics

The meta-analysis included 11 articles with 11 independent cohorts and a total of 2328 patients (Table; Table IV in the Data Supplement). A total of 6 articles reported data on LGE presence; 5 on LGE extent; and 5 on LGE location. Information on all-cause mortality and cardiac death was available in 7 and 6 studies, respectively. MACE were analyzed by 10 studies. Arrhythmic complications or development of heart failure were reported in 9 studies, whereas AM recurrence was assessed in 5 studies. Further information on the association between LGE features and the risk of developing adverse clinical outcomes for each study is provided in the Data Supplement.

#### Presence of LGE and the Risk of the Combined End Point

The association between LGE presence and the development of the combined end point was assessed in 6 studies.\textsuperscript{12,13,16,19–21} Adjustment for potential confounders was used in 4\textsuperscript{12,13,19,21} out of 6 studies. The pooled HR for LGE was 3.28 ([95% CIs, 1.69–6.39], $P<0.001$) for the combined end point. After applying the HK correction, this association retained significance ([95% CIs, 1.33–8.11], $P=0.02$; Figure 2A). Moderate heterogeneity was observed across the studies ($I^2=36.5\%$, $P=0.107$). When small (<50 participants)\textsuperscript{20,21} or lower quality studies\textsuperscript{15,21} were excluded, presence of LGE at baseline CMR scan was still related to the combined end point (pooled HR, 2.19 [95% CIs, 1.47–3.25], $P<0.001$ and pooled HR, 2.10 [95% CIs, 1.36–3.24], $P=0.001$, respectively; Table V in the Data Supplement). Accordingly, when the studies from Gräni et al\textsuperscript{19} and Schumm et al\textsuperscript{13} were excluded, the pooled result of the meta-analysis was not attenuated (pooled HR, 8.13 [95% CIs, 2.87–23.00]).

#### Extent of LGE and the Risk of the Combined End Point

Five studies\textsuperscript{14–16,19,22} provided information on the incidence of the combined end point and LGE extent at baseline CMR. Two studies compared patients with >2 LGE segments to subjects with LGE ≥2 myocardial segments.\textsuperscript{15,16} One study used a semiquantitative approach based on the number of positive LGE segments according to a 17-segment AHA model\textsuperscript{22}; 2 assessed LGE extent as a percentage of LV mass\textsuperscript{15,19}; and 1 as absolute LGE in grams.\textsuperscript{14} The pooled HR of LGE extent for the combined end point was 1.96 ([95% CIs, 1.08–3.56], $P=0.027$). The more conservative meta-analysis after the HK correction confirmed a trend toward increased risk for the combined end point (pooled HR, 1.96 [95% CIs, 0.843–4.57]; Figure 2B). Moderate to significant heterogeneity was observed across the studies ($I^2=75.6\%$, $P=0.1$). In sensitivity analyses, the exclusion of studies with sample size <50\textsuperscript{21} did not change the pooled risk estimate (pooled HR, 1.68 [95% CIs, 1.14–2.52]). Nevertheless, this association was attenuated when studies of lower quality\textsuperscript{22} or less likely diagnosis of AM\textsuperscript{19} were not considered (pooled HR, 1.66 [95% CIs, 0.896–3.09]; Table V in the Data Supplement).

#### Location of LGE and Risk of the Combined End Point

The relationship between the combined end point and LGE location was reported in 5 studies.\textsuperscript{15–17,19,23} Table displays the demographic and clinical characteristics of the participants. Anteroseptal location of LGE was associated with a 2.6-fold increased risk of the combined end point (pooled HR, 2.58 [95% CIs, 1.87–3.55], $P<0.001$ for the reference analysis). The HK method showed a similar trend (pooled HR, 2.58 [95% CIs, 1.64–4.06], $P=0.004$; Figure 2C). No significant het-
erogeneity was observed across the 5 studies of LGE localization ($I^2=0\%, \ P=0.535$). All studies in this analysis had >50 participants. When studies of lower quality or uncertain diagnosis of AM19 were removed, antero-septal location of LGE still conferred increased risk for the combined end point (pooled HR, 2.17 [95% CIs, 1.14–4.12], $P=0.018$). Inferolateral location of LGE trended toward a decreased incidence of MACE versus non-inferolateral distribution (HR, 0.50 [95% CIs, 0.21–1.20], $P=0.122$, $I^2=69.2\%, \ P=0.002$), but this nonsignificant trend was even further attenuated after the HK correction (HR, 0.50 [95% CIs, 0.15–1.73], $P=0.197$; Figure I in the Data Supplement).

**Meta-Regression Analysis**

In view of the moderate to significant heterogeneity in 2 main analyses (ie, presence and extent of LGE), we performed meta-regression analyses on the association of LGE pattern with the primary end point. We also
### Table: Main Characteristics of the Included Studies

| Author | Mean age | Male, N (%) | Abnormal troponin, N (%) | Abnormal ECG, N (%) | Number of segments with LGE, N (%) | Number of patients with LGE, N (%) | Myocardial extent of LGE (% myocardial surface area) | Inferolateral LGE, N (%) | Anteroseptal LGE, N (%) | LGE presence impact on clinical outcomes (HR/OR) | LGE extension impact on clinical outcomes (HR/OR) | LGE localization impact on clinical outcomes (HR/OR) |
|--------|----------|-------------|--------------------------|-------------------|---------------------------------|-----------------------------|----------------------------------|------------------------|------------------------|---------------------------------|---------------------------------|---------------------------------|
| Grün et al\(^{12}\) | 52 (40-54) | 63 (31.0) | 46 (22.7) | 281 (100) | 108 (53.2) | 18.2 (95%) | 4.2 (2.3-9.3) | ... | ... | HR, 8.40 (95% CIs, 1.98-35.72) | ... | ... |
| Barone-Rochette et al\(^{22}\) | 33±10 | 19 (68) | 131 (32.3) | 114 (28.3) | 203 (100) | 11.4±7.0 | 3.8±2.2 | 3.8±2.2 | 2 (1-4) | 114 (100) | 3.2 (1.6-6.5) | 1.2 (0.6-2.1) | 1.16 (95% CIs, 0.70-2.6) |
| Schumm et al\(^{13}\) | 47.9±15.5 | 178 (60) | 141 (42) | 61 (18.9) | 188 (56) | 38 (9.4) | 14 (3.7) | ... | ... | 178 (100) | 3.8 (1.5-9.7) | ... | ... |
| Sanguineti et al\(^{15}\) | 42.7±16.5 | 146 (66) | 105 (46) | 107 (46) | 203 (100) | 34 (16) | 114 (56) | 36 (15) | 114 (56) | HR, 1.23 (95% CIs, 0.74-2.04) | HR, 1.23 (95% CIs, 0.74-2.04) | HR, 1.23 (95% CIs, 0.74-2.04) |
| Chopra et al\(^{14}\) | 35±15 | 37 (80) | 32 (80) | 21 (52) | 61 (40) | 3 (7.6) | 2.2±4.4 | 2.2±4.4 | ... | 21 (34) | 21 (34) | 21 (34) | 21 (34) |
| Aquaro et al\(^{16}\) | 38±15 | 299 (73) | 155 (40) | 165 (41) | 294 (77) | 7 (18.9) | 2.3±0.7 | 2.3±0.7 | 2.3±0.7 | 2.3±0.7 | 2.3±0.7 | 2.3±0.7 | 2.3±0.7 |
| Gräni et al\(^{19}\) | 47.8±16.0 | 392 (59) | 278 (42) | 170 (51) | 392 (59) | 38 (9.3) | 15 (3.9) | ... | ... | 38 (100) | 38 (100) | 38 (100) | 38 (100) |
| Spieker et al\(^{20}\) | 41±16 | 33 (72) | 32 (70) | 28 (68) | 33 (72) | 3 (0.7) | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 |
| Lee et al\(^{21}\) | 41.5±17.5 | 22 (59) | 31 (83.8) | 21 (59) | 22 (59) | 3 (0.7) | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 | 1.4±0.4 |
| Filippetti et al\(^{23}\) | 47±12 | 54 (76) | 47 (63) | 47 (63) | 54 (76) | 47 (63) | 47 (63) | 47 (63) | 47 (63) | 47 (63) | 47 (63) | 47 (63) | 47 (63) |
| Imazio et al\(^{24}\) | 47 (42-51) | 53 (75) | 47 (63) | 47 (63) | 53 (75) | 47 (63) | 47 (63) | 47 (63) | 47 (63) | 47 (63) | 47 (63) | 47 (63) | 47 (63) |

EMB indicates endomyocardial biopsy; HR, hazard ratio; LGE, late gadolinium enhancement; and OR, odds ratio.
applied meta-regression analyses for LGE location on an exploratory basis. Among age, prevalence of male sex, traditional cardiovascular risk factors, and symptoms at presentation, we did not find variables that affected the magnitude of the association between LGE presence, location or extent, and the combined end point. Accordingly, ECG abnormalities, pericardial effusion, LV ejection-fraction or LV end-diastolic volume, sustained ventricular tachycardia, and troponin levels did not modify the association between LGE features and the combined end point occurrence ($P > 0.1$ for all). Importantly, the association of anteroseptal location of LGE with increased risk of the primary end point was not influenced by the LGE extent ($P = 0.352$).

**Publication Bias and Grading of Evidence**

The funnel plot for the association between LGE presence and the primary end point was asymmetrical at its bottom left, suggesting either possible publication bias or a true nonexistence of negative studies (Figure 3A). Regression tests for funnel plot asymmetry only partially supported a small-study effect (Egger’s test: $P = 0.025$ and Begg and Mazumdar test: $P = 0.260$). Asymmetry was also evident in funnel plots for LGE extent (Figure 3B) but not for localization (anteroseptal versus non-anteroseptal; Figure 3C). Although publication bias cannot be excluded for these variables, regression diagnostic tests showed a nonsignificant effect (Egger’s test: $P = 0.221$ and $P = 0.957$; Begg and Mazumdar test: $P = 0.264$ and $P = 0.806$ for LGE extent and distribution, respectively).

According to the Grades of Recommendation, Assessment, Development and Evaluation Working Group system, the level of certainty for the association between LGE presence and location with the risk of MACE was moderate; a low level of certainty was adjudicated for the association between LGE extent with the combined end point (Table VI in the Data Supplement).
DISCUSSION

In this meta-analysis, we provide for the first time, pooled adjusted CMR-derived estimates from 2328 patients with AM showing that LGE presence and anteroseptal location are associated with a significantly increased risk of an adverse clinical outcome. Overall, patients with AM and LGE at the CMR conducted early after clinical presentation (within 2 weeks from symptom onset) had a 3-fold increased risk of dying or developing MACE during a mean 2-year follow-up as compared with their counterparts without LGE. Patients with AM and high LGE burden trended toward having a higher likelihood of experiencing the combined end point as compared with those with no or low LGE burden. Overall, these results were shown to be consistent in a number of sensitivity analyses and were not affected by baseline patient characteristics including age, cardiovascular risk factors, troponin level, and LV function.

LGE Extent and Outcomes

The risk of experiencing the combined end point was doubled in patients with more extensive LGE (ie, >2 LV segments with LGE or LGE >10% of LV mass or LGE >17 grams) as compared with those with small or no LGE burden. As expected, the 2 studies in which LGE presence was not associated with worse outcome did not show an association between LGE burden and the combined end point (Table). However, the interpretation of this finding was hindered by (1) the heterogeneity in defining the LGE burden and (2) the diversity in methodology applied for quantifying LGE including different post-processing algorithms. Moreover, when the more restrictive HK correction was applied, the LGE burden did not remain associated with the composite end point. Overall, this finding indicates that there is a trend toward LGE extent being associated with clinical outcome, but larger studies using a standardized methodology for gauging LGE are needed to confirm this.

LGE Location and Outcomes

Anteroseptal location of LGE portended a 2-fold increased risk of dying or experiencing MACE as compared with nonanteroseptal LGE. Of note, LGE extent was comparable between anteroseptal and nonanteroseptal...
septal subgroups supporting the concept that LGE location may hold prognostic value per se. A previous study found higher troponin release, LV volumes, and greater LGE extent in the anteroseptal as compared with nonanteroseptal group. However, meta-regression analysis in our study showed an independent prognostic value of anteroseptal location of LGE in patients with AM irrespective of LGE extent and indices of LV remodeling, including LV ejection-fraction and volumes. In contradistinction, an inferolateral location trended toward a reduced incidence of the primary outcome. Previous studies in patients with AM undergoing LGE-CMR guided endocardial biopsy indicated that anteroseptal myocarditis patients are more likely to harbor human herpes virus 6 and parvovirus B19 co-infection than those with nonanteroseptal involvement.40 The natural history of human herpes virus 6 infection is characterized by a long-lasting latent infection after the first exposure in early childhood and may be associated with worse outcomes, particularly as the cardiac conduction system resides in the septum.41

Clinical Implications

Contrary to the conventional knowledge of good long-term prognosis in patients affected by AM,42 our systematic review revealed an overall incidence of mortality, life-threatening ventricular arrhythmias, heart failure, and a disease recurrence rate equating to 11.5% over a mean follow-up of 2 years. On the other hand, in contrast to Yang et al.,43 who examined left ventricular ejection fraction as a dichotomized covariate in exploratory subgroup analysis, we found that impaired left ventricular ejection fraction was not an independent predictor of the combined end point. Risk stratification of patients with AM is clinically challenging, and no reliable tools are currently available. Based on our pooled analysis, presence and anteroseptal location of LGE conferred an independent increased risk for all cause of death and MACE. However, confirmatory multicenter studies are needed to investigate whether high LGE burden and anteroseptal location LGE are independent predictors of clinical outcome and whether the adoption of these markers improves risk stratification beyond the current standard of care in patients with AM.

Limitations

Our meta-analysis has a number of limitations. First, endomyocardial biopsy-based diagnosis of AM was obtained in only a few patients of the total sample. Nevertheless, given the good diagnostic yield of CMR in inflammatory cardiomyopathy and excellent agreement between CMR and endomyocardial biopsy in patients with suspected AM,43 we think that the studies included in the meta-analysis correctly included patients with AM. Second, we included only observational studies, which have an intrinsic risk for selection bias and can detect associations but not ascribe causality. Third, the studies included in the meta-analysis presented significant heterogeneity with respect to the patient populations. However, meta-regression analyses did not suggest significant modification of our estimates by baseline characteristics, including age, sex, cardiovascular risk factors, clinical presentation or laboratory parameters. Fourth, it is important to bear in mind that the presence and the anteroseptal location of LGE were associated with the occurrence of the combined end point even after the restrictive HK correction was applied. However, when sensitivity analysis was performed, although the findings remained significant, given the residual small number of studies available, the HK-correction could not be validly applied on the resulting CIs, risking the residual possibility of a type 1 error. This emphasizes the need for further prospective studies to evaluate the mechanisms and significance of LGE presence and location. Finally, novel CMR markers such as parametric imaging and myocardial strain were not adjudicated eligible for meta-analysis in view of the scarcity of data available to date. Native T1 and extracellular volume mapping techniques are increasingly being used for diagnosis and have been incorporated into the revised Lake Louise criteria.6 However, while there is growing evidence for their diagnostic utility in AM,7 and for their prognostic significance in many other disease settings,44,45 the studies in our meta-analysis predated their widespread use for this purpose. Further work is required to prospectively assess the prognostic utility of this nascent technology in patients with AM.

Conclusions

The presence of LGE and anteroseptal location on baseline CMR in AM are important independent prognostic markers that portend an increased risk of major adverse cardiac events.

ARTICLE INFORMATION

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Disclosures

None.

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