Increased Prognostic Value of Query Amyloid Late Enhancement Score in Light-Chain Cardiac Amyloidosis

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Background: Late gadolinium enhancement (LGE) pattern is a powerful imaging biomarker for prognosis of cardiac amyloidosis. It is unknown if the query amyloid late enhancement (QALE) score in light-chain (AL) amyloidosis could provide increased prognostic value compared with LGE pattern.

Methods and Results: Seventy-eight consecutive patients with AL amyloidosis underwent contrast-enhanced cardiovascular magnetic resonance imaging. Patients with cardiac involvement were grouped by LGE pattern and analyzed using QALE score. Receiver operating characteristic curve was used to identify the optimal cut-off for QALE score in predicting all-cause mortality. Survival of these patients was analyzed with the Kaplan-Meier method and multivariate Cox regression. During a median follow-up of 34 months, 53 of 78 patients died. The optimal cut-off for QALE score to predict mortality at 12-month follow-up was 9.0. On multivariate Cox analysis, QALE score ≥ 9 (HR, 5.997; 95% CI: 2.665–13.497; P < 0.001) and log N-terminal pro-brain natriuretic peptide (HR, 1.525; 95% CI: 1.112–2.092; P = 0.009) were the only 2 independent predictors of all-cause mortality. On Kaplan-Meier analysis, patients with subendocardial LGE can be further risk stratified using QALE score ≥ 9.

Conclusions: The QALE scoring system provides powerful independent prognostic value in AL cardiac amyloidosis. QALE score ≥ 9 has added value to differentiate prognosis in AL amyloidosis patients with a subendocardial LGE pattern.

Key Words: Late gadolinium enhancement; Light-chain amyloidosis; Mortality; Query amyloid late enhancement score

Myeloma light-chain (AL) amyloidosis is characterized by extracellular deposition of pathologic insoluble β-fibrillar immunoglobulin light chains in different organs due to plasma cell dyscrasia.1 Accurate identification and stratification are crucial for optimized treatment strategies such as high-dose chemotherapy, autologous stem cell transplantation and heart transplantation.2 Cardiac involvement is the leading cause of morbidity and mortality in AL amyloidosis.3 Cardiac amyloid infiltration can be characterized as diffuse subendocardial or transmural late gadolinium enhancement (LGE) on cardiovascular magnetic resonance imaging (CMR).4 These LGE patterns have good diagnostic performance with regard to suspected cardiac amyloidosis (CA).4,5 In addition, the presence of LGE is a powerful predictor of mortality in CA.6-10 Moreover, Fontana et al showed that the transmurality of LGE pattern was associated with worst prognosis when left ventricular (LV) LGE pattern was categorized into 3 categories (none, subendocardial, and transmural).11 CA can involve not only the LV but also other cardiac chambers such as the right ventricle (RV) and atria.12,13 Therefore, classification based on the LV alone may not completely capture the extent of cardiac amyloid infiltration. Dungu et al reported on query amyloid late enhancement (QALE) score, which semi-quantified LGE in both the LV and RV.14 QALE score was originally designed to differentiate AL and transthyretin-associated (ATTR) cardiac amyloid, but the semi-quantification of the LGE including the RV may have increased prognostic value within the subtypes of cardiac amyloid. Therefore, we sought to investigate if QALE score has additional prognostic value over conventional qualitative LV LGE pattern in patients with AL CA.

Methods

Subjects
From November 2011 to October 2015, a total of 85 consecutive patients with biopsy-proven extracardiac amyloid and clinical suspicion of CA underwent CMR at West China Hospital, Sichuan University, and were followed for all-cause mortality until December 2016. Diagnosis of

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systemic amyloidosis was defined according to Congo-red staining histology and green bi-refringence under cross-polarized light in at least 1 involved organ. AL amyloidosis was confirmed on dyscrasia of monoclonal plasma cells and positive immunohistology for kappa or lambda light chains on biopsy. Cardiac involvement was defined as end-diastolic thickness of the interventricular septum >1.2 cm in the absence of any other plausible cause of ventricular hypertrophy and/or typical diffuse subendocardial or transmural LGE on CMR. The study was approved by the local Ethics Committee and written informed consent was obtained from all patients.

CMR
CMR was performed on a 3.0-T scanner (Magnetom Trio Tim; Siemens Healthineers, Erlangen, Germany) with an 8-channel phased-array body coil or 32-channel dedicated cardiac coil. SSFP cine images were acquired in consecutive short-axis views covering the LV from the base to apex and 3 long-axis views (2-, 3-, and 4-chamber) with the following parameters: repetition time (TR), 3.4 ms; echo time (TE), 1.3 ms; flip angle, 50°; field of view, 320–340 mm; matrix size, 256×144; and slice thickness, 8 mm with no gap. LGE images were acquired at 3–5 min and 10–15 min after 0.15 mmol/kg i.v. gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma, Berlin, Germany) using the inversion recovery method with phase-sensitive reconstruction (PSIR) on identical views (TR, 700 ms; TE, 1.56 ms; flip angle, 20°; matrix, 256×144). TI was optimized individually to null the normal myocardial signal using a TI scout sequence.

LV Function and Mass
Images were analyzed using commercially available software (QMass V.7.5, Medis, Leiden, The Netherlands) by 2 experienced observers (H.L. and D.Y.) blinded to clinical and biomarker information. The endocardial and epicardial borders of the LV myocardium were manually drawn in end-diastole and end-systole on the short-axis cine images following the SCMR guidelines. Volumes were derived by summation of discs, and ejection fraction (EF) was calculated accordingly. LV mass index (LVMI) was obtained by subtraction of the endocardial from epicardial volume at end-diastole, multiplied by 1.05 g/cm³, and then indexed to body surface area (BSA).

LGE Patterns
Patients were divided into 3 groups according to the extent and pattern of LGE as determined on PSIR CMR (Figure 1): no/non-specific LGE (none or focal discrete patchy LGE in short-axis slice or long-axis views that was not subendocardial pattern); subendocardial LGE (diffuse subendocardial LGE and transmurality <50% in any short-axis slice); and transmural LGE (diffuse LGE and transmurality ≥50% in any short-axis slices). The evaluation of LGE was made on consensus of 2 experienced observers (each had >3 years and 500-case experience) blinded to clinical and outcome information. In case of discrepancy between the 2 observers on the presence of LGE, a third senior CMR specialist (Y.C.) reviewed the images for final adjudication.

LGE Scoring System
The extent of LGE was scored according to a semi-quantitative score system (QALE) and expressed as a number. The QALE score was assessed on short axis LGE PSIR at the base, mid-ventricle, and apical portion. The maximum LV QALE score at each level is 4 (0, absent; 1, non-specific or non-circumferential subendocardial; 2, circumferential subendocardial; 3, non-circumferential transmural; and 4, circumferential transmural; Figure 1), corresponding to a maximum LV LGE score of 12 in 3 slices, plus 6 if RV LGE is present. The QALE score range is 0 (no LGE in the LV or RV) to 18 (global transmural LV LGE plus RV involvement).

Follow-up
The date that the CMR was performed was considered as the start date for study enrollment. Patients were prospectively followed until December 2016. The endpoint was all-cause mortality, which was assessed by 1 cardiologist (J.W.), who was blinded to all clinical results. Data for the endpoints were obtained from hospital charts and via telephone interview with patient or patient family. No patients were lost to follow-up.

Figure 1. The query amyloid late enhancement (QALE) scoring system. LGE, late gadolinium enhancement; PSIR, inversion recovery with phase-sensitive reconstruction.
Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>No apparent cardiac involvement (n=17)</th>
<th>Cardiac involvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61±10</td>
<td>60±13</td>
<td>59±10</td>
</tr>
<tr>
<td>Male</td>
<td>11 (64.7)</td>
<td>8 (66.7)</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23±3</td>
<td>23±3</td>
<td>22±4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79±14</td>
<td>82±15</td>
<td>81±10</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120±9</td>
<td>122±18</td>
<td>112±16</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77±8</td>
<td>78±13</td>
<td>71±11</td>
</tr>
<tr>
<td>NYHA class &gt;II</td>
<td>0</td>
<td>2 (16.7)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>196 (96–281)</td>
<td>1,989 (506–5,279)</td>
<td>4,787 (1,693–14,881)</td>
</tr>
<tr>
<td>cTNT (ng/L)</td>
<td>27.8 (8.0–15.3)</td>
<td>68.5 (20.1–53.6)</td>
<td>143.8 (37.1–182.7)</td>
</tr>
</tbody>
</table>

Data given as mean±SD, n (%), or median (interquartile range). *P<0.05 †vs. no apparent cardiac involvement, ‡vs. no/non-specific LGE, §vs. subendocardial LGE (Bonferroni post-hoc analysis). BMI, body mass index; cTNT, cardiac troponin T; DBP, diastolic blood pressure; LGE, late gadolinium enhancement; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

Table 2. CMR Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>No apparent cardiac involvement (n=17)</th>
<th>Cardiac involvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI (g/m²)</td>
<td>61±17</td>
<td>63±18</td>
<td>62±37</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>63±5</td>
<td>60±6</td>
<td>48±13</td>
</tr>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>66±11</td>
<td>70±15</td>
<td>70±19</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>23±5</td>
<td>30±11</td>
<td>37±14</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>7 (58.3)</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>0</td>
<td>6 (50)</td>
<td>12 (54.6)</td>
</tr>
<tr>
<td>QALE score</td>
<td>0</td>
<td>1 (0.25–2)</td>
<td>9.5 (4–11.25)</td>
</tr>
</tbody>
</table>

Data given as mean±SD, n (%), or median (interquartile range). *P<0.05 †vs. no apparent cardiac involvement, ‡vs. no/non-specific LGE, §vs. subendocardial LGE (Bonferroni post-hoc analysis). CMR, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; QALE, query amyloid late enhancement.

Statistical Analysis

Data are expressed as mean±SD or median (interquartile range). Correlation coefficients were classified as weak, *r*>0–<0.2; mild, 0.2–<0.4; moderate, 0.4–<0.6; moderately strong, 0.6–<0.8; and strong, ≥0.8. N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T were normalized before Cox proportional hazard regression models using natural logarithm. Predictive variables for outcome were estimated using univariate and stepwise multivariate Cox regression analysis. Multivariate analysis included all variables with *P*<0.05 on univariate analysis. Results are presented as hazard ratios (HR) with 95% CI. Receiver operating characteristic (ROC) curves were constructed and Youden index was used to determine optimal cut-offs for predicting the endpoint. Survival was assessed using Kaplan-Meier analysis, with *p*-values calculated by log-rank statistics. Inter-observer and intra-observer variabilities were examined for QALE score using the intra-class and inter-class correlation coefficients. Measurements were performed in a group of 20 randomly selected subjects by 1 observer, and then repeated by the same observer and a different observer in 2 weeks. All statistical analysis was performed with SPSS (version 19.0; SPSS, Chicago, IL, USA) and MedCalc for Windows (version 14.8.1; MedCalc Software, Ostend, Belgium). Statistical significance was defined as *P*<0.05 for all tests.

Results

Subjects

Patients who received previous chemotherapy (n=3) or had poor imaging quality (n=4) were excluded. The remaining total of 61 patients fulfilling the diagnostic criteria for CA and 17 patients without apparent cardiac involvement (followed separately) were included (Figure S1). Baseline clinical characteristics are listed in Table 1. There were no differences in age, sex, systolic or diastolic blood pressure, or BSA between the 4 groups. NT-proBNP and cardiac troponin T (cTnT) in the transmural LGE group were significantly increased compared with the other groups. The ratio of patients in the transmural LGE group and 11 patients in the subendocardial LGE group were in New York Heart...
Association (NYHA) functional class III–IV. The remaining patients were in NYHA functional class I or II.

CMR in the different groups is reported in Table 2. As anticipated, LVEF was significantly decreased in the transmural LGE group (adjusted P<0.05 for all comparisons). There was no significant difference in LVEF for the no apparent cardiac involvement and the non/non-specific LGE groups. The transmural LGE group had higher LVMI and LV end-systolic volume index (LVESVI) than the no cardiac involvement group and the no/non-specific LGE group (P<0.05 for all comparisons). LV end-diastolic volume index was similar between the groups (P=0.185). In patients with cardiac involvement, median QALE score increased stepwise with LGE pattern: 1.0 (IQR, 0.3–2.0) in the no/non-specific LGE group vs. 9.5 (IQR, 4.0–11.3) in the subendocardial LGE group vs. 16.0 (IQR, 14.0–18.0) in the transmural LGE group (P<0.001). The intra-observer and inter-observer intra-class correlation coefficients for QALE score were 0.89 (95% CI: 0.74–0.95) and 0.87 (95% CI: 0.69–0.95).

QALE score was moderately strongly associated with functional status according to NYHA functional class (r=0.628, P<0.001). Moderate correlations were found between QALE score and cardiac functional and structural parameters, including LVEF (r=−0.493, P=0.001), LVESVI (r=0.437, P<0.001), and LVMI (r=0.434, P<0.001). Furthermore, QALE score was moderately associated with NT-proBNP (r=0.449, P<0.001) and moderately strongly associated with cTnT (r=0.682, P<0.001; Table 3).

On ROC curve analysis (Figure 2) the QALE score cut-off of 9 yielded the largest area under the curve (AUC) of 0.822 (95% CI: 0.702–0.908; P<0.001), with a sensitivity of 90.6% and specificity of 69.0% for discriminating between survivors and non-survivors at 12-month follow-up. All patients with cardiac LGE had QALE score ≥9, while the remaining 9 patients in the subendocardial LGE group had QALE score <9. It is notable that all patients in the transmural LGE group had RV LGE. Of the patients with subendocardial LGE, QALE score ≥9 patients (n=13) were RV LGE positive, and the QALE score <9 patients (n=9) were RV LGE negative. Representative cases of non-specific LGE, subendocardial LGE with score <9, subendocardial LGE with score ≥9 and transmural LGE are given in Figure 3.

Outcomes and Survival Data
During a median follow-up of 34 months (range, 14–60 months), 53 patients died, and no patients were lost to follow-up. Five of 17 patients (29.4%) died in the no apparent cardiac involvement group, 6 of 12 (50.0%) died in the no/non-specific LGE group, 16 of 27 (72.7%) in the subendocardial LGE group, and 26 of 27 (96.3%) in the transmural LGE group. On univariate analysis, NYHA class >II, high serum NT-proBNP and cTnT, LVEF, LVMI and QALE score ≥9 were associated with death (Table 4). On stepwise multivariate Cox regression analysis including significant variables (P<0.05 on univariate analysis), QALE score ≥9 (HR, 5.997; 95% CI: 2.665–13.497; P<0.001) and logNT-proBNP (HR, 1.525; 95% CI: 1.112–2.092; P=0.009) remained the only independent predictors of death.

On Kaplan-Meier survival analysis stratified by LGE pattern (global χ²=27.56, log-rank P<0.001), the transmural LGE group had the lowest event-free survival (3.70%; Figure 4A), while the no/non-specific LGE group had the best prognosis, similar to the no apparent cardiac involvement group (event-free survival, 70.59% and 50.0%, respectively; log-rank P=0.396). On Kaplan-Meier analysis of correlations between QALE score ≥9 and survival, patients with high QALE score had significantly lower event-free survival (log-rank P<0.001; Figure 4B). And when the subendocardial LGE pattern group was further subdivided according to the QALE score cut-off of 9, the subendocardial LGE-QALE score ≥9 group had similar event-free survival to the transmural LGE group (event-free survival, 15.38% and 3.7%, respectively; log-rank P=0.113), significantly lower than the subendocardial LGE-QALE score <9 group (log-rank P<0.001; Figure 4C). The 3 groups subendocardial LGE-QALE score <9, no/non-specific LGE, and no apparent cardiac involvement had similar event-free survival (44.44%, 50.0%, and 70.59%, respectively; log-rank P=0.576).

Discussion
In this study, we used a novel semi-quantitative QALE
The subendocardial LGE-QALE score <9 group had a better prognosis, similar to that of the no apparent cardiac involvement and the no/non-specific LGE groups, whereas the subendocardial LGE-QALE score ≥9 group had a worse prognosis, similar to that of the transmural LGE group.

Cardiac amyloid deposition can cause abnormality of cardiac chamber morphology, and myocardial diastolic and systolic dysfunction.\textsuperscript{17, 21} The burden of amyloid infiltration

<table>
<thead>
<tr>
<th>Table 4. Predictors of Mortality\textsuperscript{†} in Patients With Cardiac Amyloid</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>NYHA class &gt;II</td>
</tr>
<tr>
<td>LogTroponin T</td>
</tr>
<tr>
<td>LogNT-proBNP</td>
</tr>
<tr>
<td>LVEF</td>
</tr>
<tr>
<td>LVMI</td>
</tr>
<tr>
<td>Transmural LGE</td>
</tr>
<tr>
<td>QALE score ≥9</td>
</tr>
</tbody>
</table>

\textsuperscript{†}Cox proportional hazard regression analysis. Abbreviations as in Tables 1, 2.
Accurate quantification of amyloid infiltration on LGE is challenging in most amyloid patients, because CA is typically a diffuse disease with mixing of the normal and the diseased myocardium. T1 mapping may be more sensitive than conventional LGE for identifying cardiac amyloid involvement, but T1 mapping is not widely available, and normal reference values are sequence and scanner dependent, thereby making routine clinical application difficult. Furthermore, the increased prognostic value of T1 mapping in cardiac amyloid still needs to be clarified. The presence of LGE is an important parameter in the heart is a major determinant of morbidity and mortality in patients with AL amyloidosis.\textsuperscript{5,7,22,23} Accurate identification and stratification of CA is crucial in the management of these patients. Concentration of serum biomarkers such as NT-proBNP and troponin T is useful in risk stratification.\textsuperscript{24} A number of echocardiographic parameters including longitudinal systolic strain on speckle tracking have been shown to correlate with mortality or provide prognostic information for chemotherapy.\textsuperscript{18,25,26} CMR is an excellent tool to assess cardiac structure and function and provide unique information through tissue characterization.\textsuperscript{27} Accurate quantification of amyloid infiltration on LGE is challenging in most amyloid patients, because CA is typically a diffuse disease with mixing of the normal and the diseased myocardium. T1 mapping may be more sensitive than conventional LGE for identifying cardiac amyloid involvement,\textsuperscript{28,29} but T1 mapping is not widely available, and normal reference values are sequence and scanner dependent, thereby making routine clinical application difficult. Furthermore, the increased prognostic value of T1 mapping in cardiac amyloid still needs to be clarified. The presence of LGE is an important parameter

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Survival curves according to (A) cardiac involvement in amyloid light-chain amyloidosis (P<0.001); (B) query amyloid late enhancement (QALE) score (P<0.001); and (C) cardiac involvement combined with QALE score (P<0.001).}
\end{figure}
for diagnosing and risk stratifying patients with amyloidosis. LGE is also a widely available clinical technique and its robustness has improved with the phase-sensitive inversion recovery technique.

Myocardial damage identified using LGE corresponds to the distribution of amyloid protein in the myocardium that includes all 4 chambers. In multiple studies, the presence of LGE on CMR was independently correlated with a higher risk of adverse events in patients with AL amyloidosis. In a recent review and meta-analysis by Raina et al on the prognostic role of LGE imaging in CA, LGE was associated with increased risk of all-cause mortality in patients with known or suspected CA. In another recent study, Boynton et al found that LGE pattern was related to all-cause mortality, and had greater prognostic value than the Mayo Staging System in patients with AL CA. These studies, however, were limited due to the non-quantitative nature of LGE assessment using LGE pattern, and the lack of consideration of RV LGE. Cardiac amyloid is difficult to quantify using LGE due to its diffuse infiltrative nature; therefore, LGE pattern is most frequently used. LGE pattern, however, does not provide further prognostic differentiation in patients with less than transmural infiltration of amyloid. In addition, RV infiltration is not accounted for. In the QALE system used in the present study, LGE extent is scored based on 3 short-axis slices and the presence of RV LGE. It is easy to use without the need for specialized post-processing software.

Consistent with previous CMR studies, the present study also confirmed that LGE is a strong predictor of mortality after adjustment for known prognostic factors including LV parameters, RV parameters and NYHA functional class. On multivariate Cox analysis, the QALE scoring system was a powerful independent predictor for mortality in AL amyloidosis and was able to further stratify patients with subendocardial LGE. On Kaplan-Meier analysis, QALE score ≥9 in patients with the subendocardial LGE pattern had an increased risk of mortality compared with QALE score <9. QALE score ≥9 represents more diffuse subendocardial infiltration and/or RV infiltration in some patients with subendocardial LGE pattern. Because all QALE score ≥9 patients were RV LGE positive and the QALE score <9 patients were RV LGE negative in this subgroup, RV involvement was thus the major contributor for determination of QALE score, and further stratification of prognosis in this subgroup. This indicates that the combination of LGE pattern and the semi-quantitative QALE scoring system provides better risk stratification of survival in patients with AL amyloidosis and the subendocardial LGE pattern.

Study Limitations
This was a single-center study with a relatively limited sample size in the subendocardial LGE group. Future clinical studies involving multiple centers with larger sample size are warranted to verify this risk stratification strategy. Second, data regarding cardiovascular outcomes (stroke, thromboembolism, new episodes of atrial or ventricular arrhythmia, permanent pacemaker insertion) were not available, thus limiting the ability to assess the predictive value of those events.

Clinical Implications
LGE is a powerful method to diagnose and determine prognosis in CA. QALE score is a simple technique to semi-quantify myocardial amyloid and adds prognostic value in patients with the subendocardial pattern of LGE.

Conclusions
The QALE scoring system can play an important role in predicting survival in AL amyloid patients. The QALE scoring system has increased prognostic value with regard to AL amyloid patients with the subendocardial LGE pattern.

Disclosures
The authors declare no conflict of interest.

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References


**Supplementary Files**

**Supplementary File 1**

*Figure S1.* Subject selection.

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-17-0464