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RESEARCH LETTER

Assessment of Left Ventricular, Right Ventricular, and Left Atrial Strain in Light-Chain Amyloidosis

Primary light chain (AL) amyloidosis is characterized by extracellular deposition of misfolded proteins overproduced by clonal plasma cell dyscrasia. Cardiac involvement represents an important prognostic determinant of survival. Traditionally, serum biomarkers have been used for staging and prognosis (1). Recent research has focused on cardiac imaging techniques such as speckle-tracking echocardiography–derived strain for predictors of adverse outcomes (2). However, few studies have assessed the association of baseline strain parameters with survival in patients without clinical heart failure (HF) who have undergone autologous hematopoietic stem cell transplantation (HSCT). This has important clinical implications because centers use symptoms and biomarkers of cardiac dysfunction when considering HSCT eligibility. The aim of this study was to evaluate the association of baseline echocardiographic left atrial (LA), left ventricular (LV), and right ventricular (RV) strain in patients with AL amyloidosis without baseline clinical HF who underwent HSCT with post-HSCT survival.

This retrospective study included 30 consecutive patients with histologically confirmed AL amyloidosis without clinical HF, who underwent HSCT at a single, quaternary care institution between May 2003 and September 2012. Institutional review board approval was obtained for the study. Participants were excluded if they had their first transthoracic echocardiogram after stem cell transplantation (n = 4). No patient had clinical HF before HSCT. Follow-up time began at the HSCT date. Baseline characteristics were summarized using the median with 25th and 75th percentiles (quartile [Q] 1 to Q 3) for continuous variables or percentages for categorical data. Using post-processing EchoInsight software (Epsilon Imaging, Ann Arbor, Michigan), baseline LA reservoir strain (RS), LV global longitudinal strain (GLS), and RV free-wall strain (FWS) pre-HSCT were measured by a cardiologist blinded to the outcome of interest and classified with pre-specified abnormal cut point values of 39%, −18%, and −25% based on literature review, respectively.

Kaplan-Meier analyses were used to evaluate differences in overall survival between participants with normal and abnormal baseline strain parameters. Log-rank tests were used to examine differences in survival Kaplan-Meier curves. Cox proportional hazards models tested the association between each continuous strain parameter as a predictor of mortality, with adjustment for age and systolic blood pressure. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. A 2-sided alpha of 0.05 was used to determine statistical significance. All analyses were performed using R Version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

After exclusion, a total of 26 participants were included in this study. Over a median follow-up of 5.5 years (Q1 to Q3: 3.0 to 7.3 years), 8 participants died (31%). Median age was 57 years (Q1 to Q3: 53 to 65 years), 69% were men, baseline ejection fraction was 65% (Q1 to Q3: 60.5% to 70.4%), and baseline brain natriuretic peptide (BNP) was 132 pg/ml (Q1 to Q3: 46.0 to 300.0 pg/ml). Median time from transthoracic echocardiography to HSCT was 43 days (Q1 to Q3: 29.0 to 97.5 days). Organ involvement was most commonly renal (92%), and 46% of participants had subclinical cardiac involvement defined as an elevated BNP above the reference range; however, no participant had a history of clinical HF or volume overload that required diuretics. Chronic kidney disease (35%) was the most common comorbidity. All patients included in this study received a high dose of melphalan for conditioning chemotherapy per institutional protocol.

We found significant differences in overall survival between normal and abnormal values of LV GLS (p = 0.030) and RV FWS (p = 0.012) (**Figure 1**). Mean baseline values of those who were alive versus those who died was −17.0% versus −13.4% for LV GLS and −21.7% versus −17.6% for RV FWS, respectively. Using Cox proportional hazards modeling, we estimated the unadjusted hazard associated with mortality to be 14%, 16%, and 14% lower for a 1-U difference in absolute LA RS (HR: 0.86; 95% CI: 0.76 to 0.98; p = 0.023), absolute LV GLS (HR: 0.84; 95% CI: 0.72 to 0.97; p = 0.018), and absolute RV FWS (HR: 0.86;

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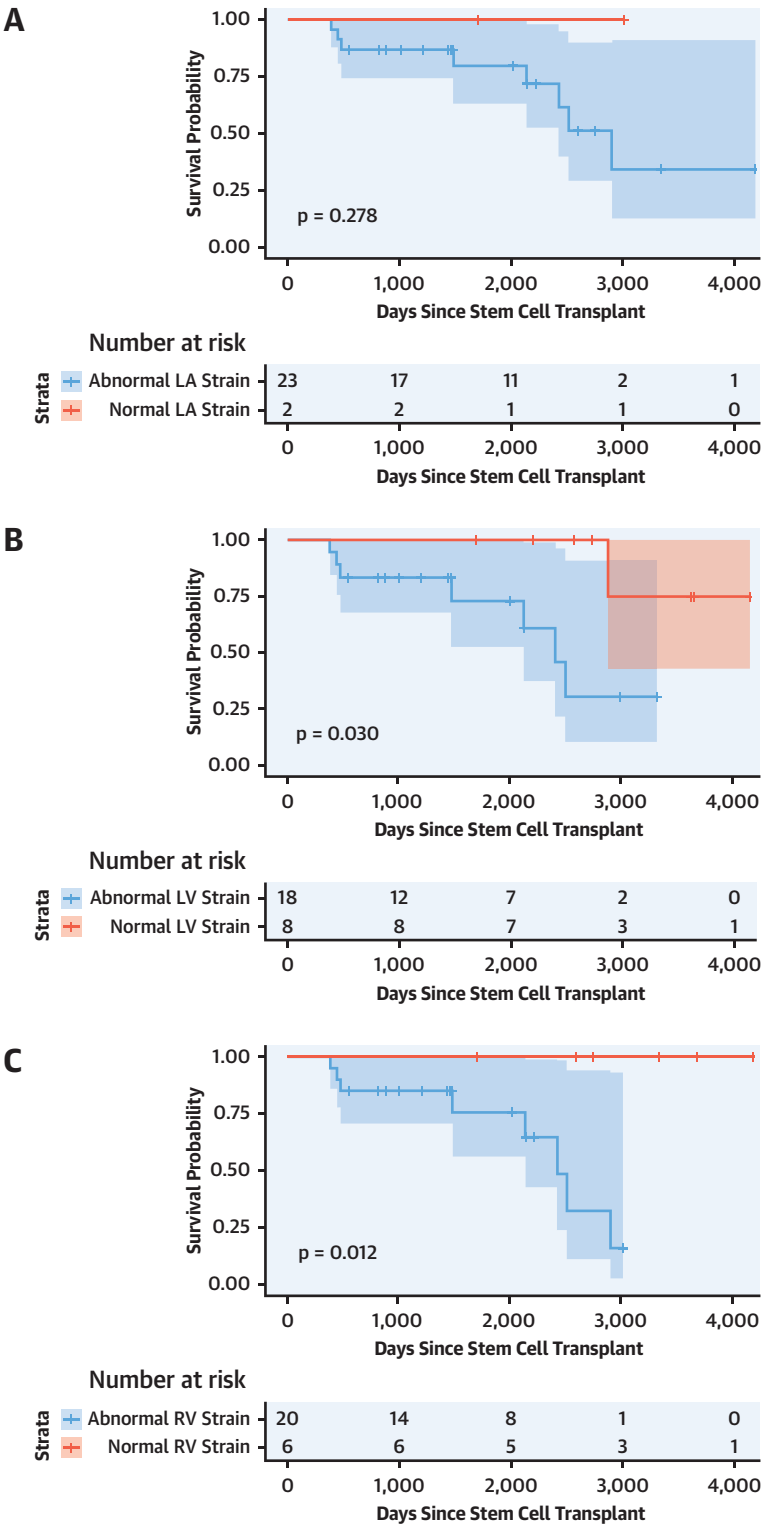
FIGURE 1 Kaplan-Meier Survival Analysis Post-HSCT



Kaplan-Meier survival curves in participants with normal and abnormal baseline 2-dimensional speckle tracking echocardiography. **(A)** Left atrial reservoir strain (LA RS), **(B)** left ventricular global longitudinal strain (LV GLS), and **(C)** right ventricular free-wall strain (RV FWS). Time was determined as days from hematopoietic stem cell transplantation (HSCT). **Shaded regions** represent 95% confidence intervals.

95% CI: 0.75 to 1.00; p = 0.045), respectively. After adjusting for age and blood pressure, the association remained significant for LA RS (HR: 0.87; 95% CI: 0.76 to 0.99; p = 0.037) and RV FWS (HR: 0.93; 95% CI: 0.69 to 0.99; p = 0.036), whereas LV GLS was of borderline statistical significance (HR: 0.87; 95% CI: 0.75 to 1.00; p = 0.054).

To our knowledge, this was the first study to show a relationship between multichamber baseline strain parameters and post-HSCT survival in patients with AL amyloidosis without clinical HF pre-HSCT. We found abnormal baseline LV GLS and RV FWS to be associated with mortality. In addition, we observed higher absolute values of LA RS to be associated with improved survival. These findings confirm and add to the existing literature demonstrating that echo-derived strain is associated with survival in AL amyloidosis post-HSCT (2–4).

Previous studies included patients with AL amyloidosis both with and without clinically overt cardiac dysfunction and were not specific to a cohort that underwent HSCT. Our study supported that, even in the absence of clinical HF, strain parameters were associated with post-HSCT mortality. Furthermore, these data suggested LA strain pre-HSCT might be a clinical marker of prognosis. Larger studies are needed to confirm these findings.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* author instructions page.

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