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Serial assessment of cardiothoracic ratio as a predictor of progression from stage B to stage C heart failure in asymptomatic patients with cardiac diseases

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Stage B is a pre-stage to symptomatic clinical heart failure (HF) with immense focus from clinicians and researchers because preventing patients from becoming symptomatic with HF has vast implications for mortality and morbidity [1,2]. Several clinicians use the cardiothoracic ratio (CTR) to evaluate cardiomegaly on chest X-ray, and recent guidelines provide class 1 recommendations as a useful initial diagnostic test. Echocardiography should be performed during the initial evaluation to assess cardiac structure and function, followed by computed tomography (CT) or magnetic resonance imaging (MRI). In daily practice, these imaging parameters may permit the early identification of patients at an increased risk of developing symptomatic HF. Therefore, the present study was designed to investigate whether serial assessment of CTR and left ventricular end-diastolic diameter (LVDD) on echocardiography could be used to estimate the risk of new-onset HF in 5,126 patients with Stage B HF registered in the CHART-2 Study [3].

The CHART-2 Study is a multicenter, hospital-based prospective observational study in which consecutive patients older than 20 years with significant coronary artery disease and those at stages B–D according to the guidelines of AHA/ACC were enrolled [2–4]. Enrollment was initiated from October 2006 to March 2010. All information, including medical history, laboratory data, and echocardiography data, was recorded in a database at the time of enrollment. Annual follow-ups were conducted by clinical research coordinators by reviewing medical records, surveys, and telephone interviews. Stage B was defined by echocardiographic and clinical findings as follows; enlarged LVDD (LVDD $\geq$ 55 mm), reduced left ventricular ejection fraction (LVEF $\leq$ 50%), thickened interventricular septum (>12 mm) and/or thickened left ventricular posterior wall (>12 mm), valvular heart disease, wall motion abnormalities, congenital abnormalities, and previous cardiac surgery (such as coronary artery bypass grafting) [3]. The included patients did not present with current or previous symptoms or signs of HF. Chest radiography was performed annually for more than 8 years. CTR and echo parameters were measured according to usual care in each practice; the measurements were not standardized. New-onset HF was defined as a composite of HF progression presenting with clinical symptoms of HF or the addition of diuretics, ACEIs/ARBs, beta-blockers, intravenous catecholamine administration, hospitalization for HF, and HF death. A *t*-test and two-way mixed analysis of variance (ANOVA) were used to detect the differences in the distribution of CTR at the baseline and across all time points, respectively. CTRs were calculated before the development of HF in each patient. We further employed a generalized linear mixed model to adjust for baseline characteristics when comparing differences in CTR distribution between patients with and without new-onset HF. All statistical analyses were performed using R Language (version 4.2.1) The present study conformed to the Declaration of Helsinki and was approved by the local ethics committees of the 24 participating hospitals.

The mean (SD) age of the 5,126 patients with Stage B was 67.7 (12.0) years, and 1,439 (29.1%) were women. Of these total patients, 775 (16.2%) had LVDD $\geq$ 55 mm, 523 (10.9%) had LVEF $\leq$ 50%, 1,317 (27.7%) had thickened interventricular septum (>12 mm) and/or thickened left ventricular posterior wall (>12 mm), 382 (7.5%) had valvular heart disease (VHD), 1,124 (23.4%) had wall motion abnormalities, 103 (2.0%) had congenital abnormalities, 557 (10.9%) had undergone a cardiac surgery previously, and 1,238 (24.2%) had atrial fibrillation. Of the 382 patients with VHD, 231, 126, and 25 had aortic, mitral, and combined valvular diseases, respectively. The CTRs for aortic stenosis, aortic regurgitation, mitral stenosis, and mitral regurgitation were 53.1%, 53.6%, 56.2%, and 53.5%, respectively. Of the 103 patients with congenital abnormalities, 29 had atrial septal defects, 32 ventricular septal defects, 6 tetralogy of Fallot, and 17 other abnormalities. The remaining 19 patients had concomitant lesions. The mean CTR was 52.1 (6.2) in congenital abnormalities. Over a median (IQR) of 10.1 (5.3–12.0) years, 971 (18.9%) patients experienced new-onset HF. Baseline CTR values were significantly higher in patients with new-onset HF than those without HF (53.3 $\pm$ 6.2% vs. 50.1 $\pm$ 5.4%, $P < 0.001$) (Fig. 1**A**). The baseline LVDD values were clinically similar in both groups (48.3 $\pm$ 6.6 mm vs. 49.7 $\pm$ 7.7 mm, $P < 0.001$). The Spearman's Rho between LVDD and CTR was 0.07 ($P < 0.001$). Furthermore, annual increase in CTR was higher in patients with new-onset HF than in those without HF, in whom change was minimal over follow-up periods (+0.47 $\pm$ 3.55% vs. + 0.13 $\pm$ 3.31%, $P < 0.001$) (Fig. 1**B**). After adjusting for age, sex, and hypertension, the difference between the patients with new-onset HF and those without HF remained significant ($P = 0.005$). When setting the outcome as a composite of hospitalization for HF and HF death as a "hard" endpoint, the trends between the

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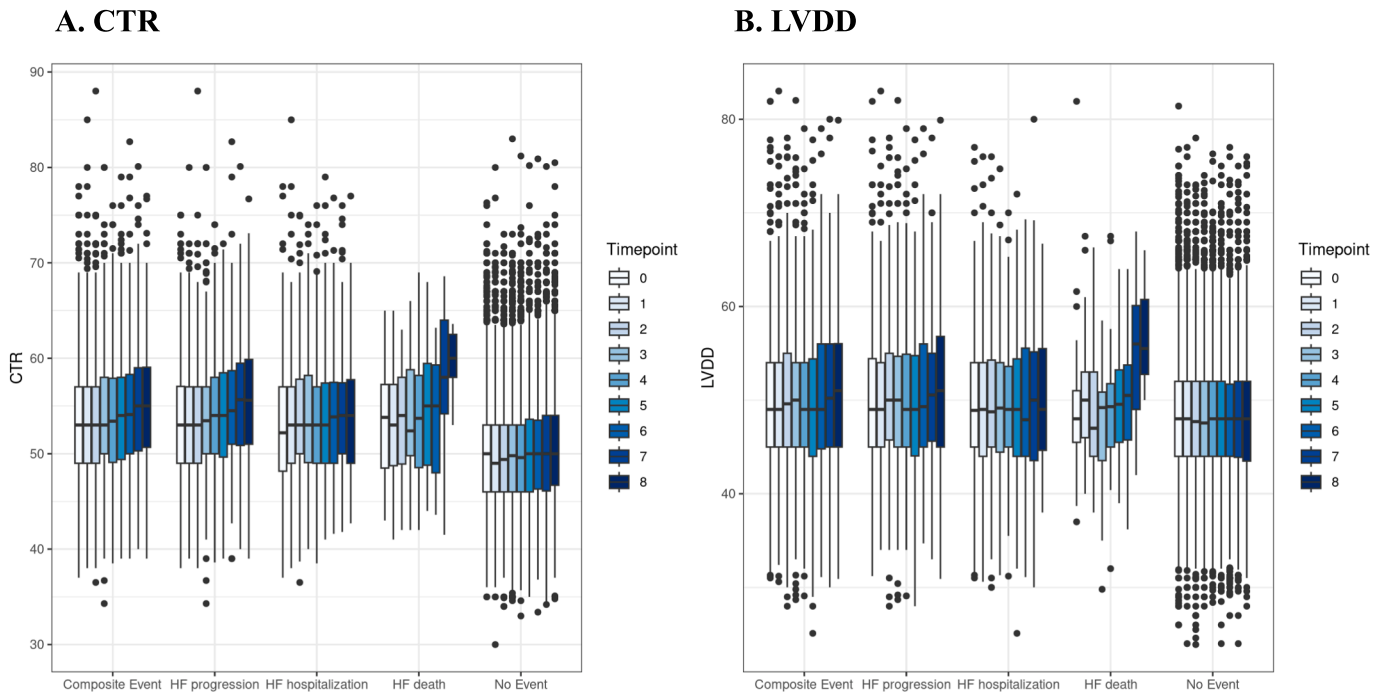

Fig. 1. Distribution of cardiothoracic ratio (CTR; A) and left ventricular end-diastolic diameter (LVDD; B) from baseline to each time point (every year over 8 years). The composite event includes heart failure (HF) progression, hospitalization for HF, and HF death.

increase in CTR and the outcome remained significant (+0.52 ± 3.65% vs. + 0.15 ± 3.31%, P < 0.001).

The present study with multicenter, prospective, and longitudinal fashion demonstrated that a combination of baseline CTR > 53% and an increase in CTR > 0.5% per year was a prognostic risk factor in asymptomatic patients with cardiovascular diseases and that serial assessment can be used for risk assessment for new-onset HF. Given the difference of +0.5% per year in CTR to predict HF, it is important to understand the gradual increase in CTR over a long period to identify individuals at high risk of developing HF. Chest radiography is the most widely used modality for initial evaluation of heart disease in clinical practice because of its accessibility and reliability. The 2022 AHA/ACC/HFSA Guidelines recommend chest radiography for evaluating patients presenting with signs and symptoms of HF, and no recommendation was provided for asymptomatic patients considering the limited sensitivity and specificity to determine the specific cause or presence of HF.[2] Our data suggest that serial chest X-ray assessments in asymptomatic patients may be useful in predicting HF progression. Demonstrating the superiority of CTR was beyond the scope of this study. However, the long-term increase in CTR revealed a stronger correlation with new-onset HF than with LVDD. Therefore, our results may be useful in regions with limited access to other imaging modalities.

In conclusion, we demonstrate that a combination of baseline CTR > 53% and an increase in CTR > 0.5% per year was a prognostic risk factor in asymptomatic patients with cardiovascular diseases, suggesting the clinical importance of serial assessment of CTR for detecting new-onset HF.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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