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Correlation of rheumatoid and cardiac biomarkers with cardiac anatomy and function in rheumatoid arthritis patients without clinically overt cardiovascular diseases: A cross-sectional study

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ABSTRACT

Background: Cardiac biomarkers have been shown to be related to cardiac abnormalities; nonetheless, few studies have confirmed the association between cardiac and rheumatoid biomarkers in rheumatoid arthritis (RA) patients. This study assessed the correlation of rheumatoid and cardiac biomarker levels with cardiac anatomy and function and explored the interaction between cardiac and rheumatoid biomarkers in RA patients without clinically overt cardiovascular diseases.

Methods: A cross-sectional study was conducted among RA patients aged 18–65 years without other connective tissue diseases, overlap syndrome, heart disease, or renal failure were included. Main cardiac and rheumatoid biomarkers, including high-sensitivity troponin T (hsTropT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), rheumatoid factor, and anti-cyclic citrullinated peptide antibody (ACPA), were collected. Echocardiography was performed to examine cardiac anatomy and function.

Results: The mean left ventricular mass index (LVMI) was 80.8 g/sqm, and the relative wall thickness was 0.4. The mean left ventricular ejection fraction was 70.3%. The hsTropT levels showed a weak positive correlation with LVMI and E/e' ratio and a very weak correlation with E/A ratio. Interaction effect between hsTropT and ACPA on LVMI was found in univariate analysis, not in multivariate analysis. Higher systolic blood pressure (SBP) and the use of non-steroidal anti-inflammatory drug (NSAID) increased the LVMI. Only age was related to the E/e' increase.

Conclusion: The effect of hsTropT on LVMI was probably modified by ACPA in RA patients without clinically overt cardiovascular diseases. Age, SBP, and NSAID use among RA patients should be taken into account due to their relations to cardiac abnormalities.

1. Introduction

Rheumatoid arthritis (RA) is the most common type of chronic inflammatory arthritis. Chronic inflammation in RA leads to permanent joint damage, disability, and premature death [1], and the mortality rate has been reported to be higher in RA patients than in the general population [2,3]. Cardiovascular disease (CVD) is a major cause of death in RA patients [2,4], and cardiovascular mortality is increased by 20–50% in RA patients, compared with that in patients without RA [5,6]. Moreover, the incidence of myocardial infarction, arrhythmia, pericardial disease, and left ventricular (LV) dysfunction is higher in RA patients than in the general population [4,7,8]. Additionally, RA patients have significantly worse LV systolic and diastolic function, especially patients with active disease [9,10]. Some biomarkers such as high-sensitivity troponin T (hsTropT) and B-type natriuretic peptide (BNP) are evidently related to abnormal heart structure and function, which are mediated by chronic myocardial injury [11,12].

Both hsTropT and BNP are found in patients with hypertrophic cardiomyopathy [13], which can be explained by chronic cardiac injury that causes an elevation in cardiac biomarker levels in malignant LV

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hypertrophy and subclinical cardiac injury in the general population [14]. In hypertensive patients, hsTropT and BNP levels are related to an abnormal LV structure [15,16]. Furthermore, cardiac troponin and BNP levels have been reported to increase in patients with myotonic dystrophy or chronic kidney disease and in the subclinical general population with abnormal LV systolic and diastolic function [17–19]. Similarly, cardiac troponin has been shown to be related to indolent myocardial injury in RA patients [20].

In RA patients, rheumatoid factor (RF) and anti-cyclic citrullinated protein/peptide antibody (ACPA) are common rheumatoid-related biomarkers that function as antigenic stimuli [21]. ACPA and RF are autoantibodies that arise as a result of the loss of tolerance to citrulline-containing proteins, which incurs a risk of sustained inflammatory cascade by RF-producing B cells, leading to tissue damage, including extra-articular manifestations [22]. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are also associated with inflammation and active diseases [23]. RF is an independent risk factor for LV dysfunction in heart failure among RA patients with cardiovascular disease after adjustment for other risk factors [24,25], as well as in RA patients with asymptomatic ventricular dysfunction [26].

Previous studies reported abnormalities in LV and right ventricular structure and function in RA patients without clinically overt cardiovascular diseases, which may be related to positive RF [27,28]. Nonetheless, the explanation for these findings remains unclear. We hypothesized that rheumatoid and cardiac biomarkers are associated with abnormal cardiac anatomy and function. Therefore, this study aimed to assess the correlation of rheumatoid and cardiac biomarker levels with cardiac anatomy and function in RA patients without clinically overt cardiovascular diseases and explore the interaction effect between rheumatoid and cardiac biomarkers and other associated factors on cardiac anatomy and function.

2. Methods

A cross-sectional study was conducted from May to November 2018 at a rheumatology clinic in Songklanagarind Hospital, a tertiary-care university hospital located in southern Thailand. The study proposal was submitted to and approved by the Human Ethical Research Committee of the Prince of Songkla University Faculty of Medicine (REC. 60-257-14-1), and informed consent was obtained from all participants included in the study.

A total of 299 eligible participants were RA patients aged at least 18 years who were diagnosed using the 1987 American College of Rheumatology (ACR) criteria [29] or the 2010 ACR/European League Against Rheumatism criteria [30]. The exclusion criteria were as follows: age $>$ 65 years (owing to the increased incidence of cardiovascular events in those aged $>$ 65 years) [31] and diagnosis of other connective tissue diseases, overlap syndrome, heart disease (previous or current clinical signs of heart disease diagnosed by a cardiologist, including CVD, cardiomyopathy, valvular heart disease, arrhythmia, and congestive heart failure), or renal failure (glomerular filtration rate $<$ 30 mL/min or renal replacement therapy). Thirty patients were excluded as they were unwilling to participate in the study.

The sample size was calculated using the correlation formula, considering the correlation coefficient between cardiac biomarkers and cardiac anatomy. We used BNP as a cardiac biomarker and LV mass index (LVMI) as a determinant of cardiac anatomy, which showed a correlation coefficient of 0.3 [32]. Considering a 95% confidence interval and 90% power, at least 73 RA patients were required. In order to obtain sufficient samples, BNP was chosen for the sample size calculation because it showed a lower correlation with LVMI than hsTropT.

The main outcome measures were cardiac anatomy and function, which were measured using transthoracic echocardiography performed by two experienced cardiology board-certified physicians using GE Vivid E9 (GE Healthcare, Wauwatosa, WI, USA) with an M5S probe in accordance with a predefined protocol.

Main parameters of cardiac anatomy were relative wall thickness (RWT) and LVMI. RWT was calculated based on posterior wall thickness (PWT). LVMI was calculated by dividing the LV mass by the body surface area. The LV mass was calculated from end-diastolic estimates of PWT, septal wall thickness (SWT), LV internal diameter at end-diastole (LVIDD), and at end-systole (LVIDS) using Devereux's formula. PWT, SWT, LVIDD, and LVIDS were measured in millimeters.

Main parameters of cardiac function were considered as systolic left ventricular function measured by left ventricular ejection fraction (LVEF) measured using Teicho's method and modified Simpson's biplane method [33] and diastolic left ventricular function measured by deceleration time (DT), ratio of early filling and atrial filling velocities on transmitral Doppler (E/A), and ratio of early filling velocity on transmitral Doppler and early relaxation velocity on tissue Doppler (E/e'). E/e' and E/A were calculated by dividing E by e' and A, respectively. DT was defined as the time interval from the peak of the early filling velocity wave to its projected baseline [34,35]

The main exposures were cardiac (hsTropT and NT-proBNP) and rheumatoid (RF and ACPA) biomarkers. Serum hsTropT and proBNP (cobas e411; Roche Diagnostics, Indianapolis, IN, USA) levels were reported in ng/L and pg/mL, respectively. RF was measured using the turbidimetric method, with a cut-off point of $>$ 12.5 IU/mL being defined as positive. ACPA was measured using the chemiluminescent microparticle immunoassay method, with a cut-off point of $>$ 5 IU/mL being defined as positive.

Other independent variables were age, blood pressure, underlying disease, basic laboratory results, duration of RA, extra-articular manifestations, rheumatoid activity, treatment, and disease-modifying antirheumatic drugs (DMARDs). Rheumatoid activity was evaluated using the standard Disease Activity Score-28 (DAS28), which was calculated using ESR. Patients were categorized into the following 4 groups: DAS28 $>$ 5.1, high disease activity; DAS28 $>$ 3.2 $\leq$ 5.1, moderate disease activity; DAS28 $\geq$ 2.6 and $\leq$ 3.2, low disease activity; and DAS28 $<$ 2.6, remission [36]. Additionally, routine clinical chemistry data were collected.

All RA patients who visited the rheumatology clinic in the study setting were checked against the eligibility criteria and invited to participate in the study. After the patients provided written consent, they were interviewed to gather demographic, clinical, and laboratory data on the same day as enrollment. Echocardiography was scheduled within 1 week after enrollment. All data were confidentially recorded and analyzed in accordance with the ethics committee-approved protocol.

All analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) [37]. Baseline characteristics were presented as frequency and percentage, mean with standard deviation (SD), or median with interquartile range, as appropriate. The correlation of cardiac markers (hsTropT and NT-proBNP) with cardiac anatomy and function was analyzed using Spearman's rank correlation (rho coefficients). Cardiac anatomy (LVMI and RWT) and function (LVEF, E/A, DT, E/e') in four groups of either positive or negative biomarkers (RF negative / ACPA negative, RF negative / ACPA positive, RF positive / ACPA negative, RF positive / ACPA positive) were analyzed using Analysis of Variance (ANOVA) or the Kruskal Wallis test for continuous variables, depending on the distribution of data. Because BNP showed a negligible correlation [38] with cardiac anatomy and function, only hsTropT was tested for the interaction with rheumatoid markers to determine LVMI and E/e' using univariate and multivariate linear regression models. The main exposures and other variables measured in this study was included in the first model and backward stepwise method were used to identify the significant variables. Significant variables adjusted for main cardiac and rheumatoid biomarkers as well as the interaction of hsTropT and rheumatoid markers were kept in the final model. Significance level was set at a p-value $<$ 0.05.

Table 1
Characteristics and clinical data of the included RA patients without clinically overt cardiovascular diseases.

	Patients (N = 109)
Age (years), median (IQR)	53 (47, 58)
Female (n, %)	105 (96.3)
BMI, median (IQR)	23.8 (21.7, 27.5)
SBP, mean (SD)	129.3 (15.4)
DBP, mean (SD)	74.9 (9.6)
Past medical history	
Smoker	
Former	7 (6.4)
Current	2 (1.8)
Never	100 (91.7)
Hypertension	20 (18.3)
Diabetes mellitus	7 (6.4)
Dyslipidemia	45 (41.3)
Family history of	
Myocardial infarction (n, %)	10 (9.2)
Old cerebrovascular accident (n, %)	14 (12.8)
RA and treatment	
Duration of RA (months), mean (SD)	106.8 (77.1)
Presence of rheumatoid nodules	18 (16.5)
Disease Activity Score-28	
Remission	23 (21.1)
Low disease activity	16 (14.7)
Moderate disease activity	56 (51.4)
Severe disease activity	14 (12.8)
ESR (mm/h), mean (SD)	46.5 (30)
CRP (mg/L), mean (SD)	4.3 (5.4)
NSAID use (n, %)	36 (33.0)
Prednisolone use (n, %)	59 (54.1)
DMARDs	
DMARD use, mean (SD)	1.8 (0.9)
Methotrexate use (n, %)	102 (93.6)
Sulfasalazine use (n, %)	36 (33)
Hydroxychloroquine use (n, %)	29 (26.6)
Azathioprine use (n, %)	1 (0.9)
Chloroquine use (n, %)	2 (1.8)
Leflunomide use (n, %)	30 (27.5)

RA, rheumatoid arthritis; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAID, non-steroidal anti-inflammatory drug; DMARD, disease-modifying anti-rheumatic drug.

Table 2
Identification of rheumatoid and cardiac biomarkers in RA patients without clinically overt cardiovascular diseases.

	Patients (N = 109)
RF positive (n, %)	63 (57.8)
ACPA positive (n, %)	69 (63.3)
hsTropT (ng/L), mean (SD)	5.6 (2.9)
<14	102 (96.2)
≥14	4 (3.8)
NT-proBNP (pg/mL), mean (SD)	74 (69.3)
<125	93 (87.7)
≥125	13 (12.3)

RA, rheumatoid arthritis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; hsTropT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide

3. Results

Of 299 patients with eligible criteria, 190 patients were excluded due to age > 65 years (n = 48), diagnosis of other connective tissue diseases, cardiovascular disease (n = 80), renal failure (n = 32), and unwilling to participate in the study (n = 30). The clinical characteristics of 109 RA patients are summarized in Table 1. The age of the patients ranged from 31 to 65 years, and 96.3% of the RA patients were women. Obesity, hypertension, hyperlipidemia, and diabetes were identified in 16%, 18.3%, 41.3%, and 6.4% of patients, respectively. The proportion of patients with moderate to severe disease activity was higher than that of patients with low disease activity and remission, as classified by DAS28 (64.2% vs. 35.8%). The mean duration of RA was 106.8 months. Rheumatoid nodules were present in 16.5% of patients. Overall, 33% of patients received non-steroidal anti-inflammatory drugs for symptom control, whereas 54% used steroids. Methotrexate was the mainstay DMARD (93.6%). None of the patients were treated with gold or biological agents.

Table 2 presents the rheumatoid and cardiac biomarkers in RA patients without clinically overt cardiovascular diseases. Of these patients, 57.8% and 63.3% had positive RF and ACPA, respectively. The ESR and CRP levels were 46.5 mm/hour and 4.3 mg/L, respectively. The mean hsTropT and NT-proBNP levels were 5.6 ng/L and 74 pg/mL, respectively. Most patients had a lower cut-off point for both hsTropT and NT-proBNP levels (96% and 87.7%, respectively).

Table 3 shows the cardiac anatomy and function in RA patients without clinically overt cardiovascular diseases. LVMI ranged from 39.45 to 160.18 gm/sqm (mean ± SD: 80.8 ± 20.1), whereas LVEF ranged from 57% to 85% (mean ± SD: 70.3 ± 6.1). Table 4 shows the correlations of cardiac biomarkers with cardiac anatomy and function. hsTropT showed a weak positive correlation with LVMI and E/e' and a very weak negative correlation with the E/A ratio. In contrast, NT-proBNP showed very weak correlations with cardiac anatomy and function measured.

Table 3
Details regarding cardiac anatomy and function in RA patients without clinically overt cardiovascular diseases.

	Patients (N = 109) Mean (SD)
Anatomy	
SWT (mm)	8.9 (1.7)
PWT (mm)	9.2 (3.5)
LVIDD (mm)	43.7 (5.3)
RWT (mm)	0.4 (0.1)
LVMI (gm/sqm)	80.8 (20.1)
Function	
LVEF	70.3 (6.1)
DT (ms)	210.1 (48.8)
E/A	1.2 (0.4)
E/e'	9.3 (2.8)

RA, rheumatoid arthritis; SWT, septal wall thickness; PWT, posterior wall thickness; LVIDD, left ventricular diastolic diameter at end-diastole; RWT, relative wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; DT, deceleration time; E/A, early filling and atrial filling velocities on transmitral doppler; E/e', early filling velocity on transmitral Doppler and early relaxation velocity on tissue Doppler

Table 4
Correlations of cardiac biomarker and cardiac anatomy and function in RA patients without clinically overt cardiovascular diseases.

	Correlation coefficient (rho)	
	hsTropT	NT-proBNP
Anatomy		
RWT (mm)	0.11	0.10
LVMI (gm/sqm)	0.25	0.11
Function		
LVEF(%)	0.04	0.15
DT (ms)	−0.08	−0.17
E/A	−0.19	0.10
E/e'	0.26	−0.05

RA, rheumatoid arthritis; hsTropT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RWT, relative wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; DT, deceleration time; E/A, early filling and atrial filling velocities on transmitral Doppler; E/e', early filling velocity on transmitral doppler and early relaxation velocity on tissue Doppler.

Table 5
Association of rheumatoid biomarkers with cardiac anatomy and function in rheumatoid arthritis patients without clinically overt cardiovascular diseases.

Cardiac anatomy and function	RF - / ACPA -	RF - / ACPA +	RF + / ACPA -	RF + / ACPA +	p-value
	n = 11	n = 35	n = 29	n = 34	
RWT, mean (SD)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.112
LVMI, mean (SD)	81.7 (32.3)	80.6 (18.8)	81 (20.7)	83.4 (20.9)	0.956
LVEF, mean (SD)	72.2 (4.1)	70 (7.1)	69.7 (5.8)	70.3 (5.9)	0.718
DT, median (IQR)	220 (189.5,272.5)	214 (194.5,250.5)	188 (169.0,222.0)	201.5 (183.2,230.0)	0.076
E/A, median (IQR)	1.3 (0.8,1.3)	1.2 (0.8,1.5)	1.2 (0.9,1.4)	1.2 (0.8,1.4)	0.944
E/e', mean (SD)	8.2 (1.8)	9.8 (2.3)	9.4 (2.9)	9.1 (3.3)	0.377

-, negative; + positive, RA, rheumatoid arthritis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; RWT, relative wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; DT, deceleration time; E/A, early filling and atrial filling velocities on transmitral doppler; E/e', early filling velocity on transmitral Doppler and early relaxation velocity on tissue Doppler.

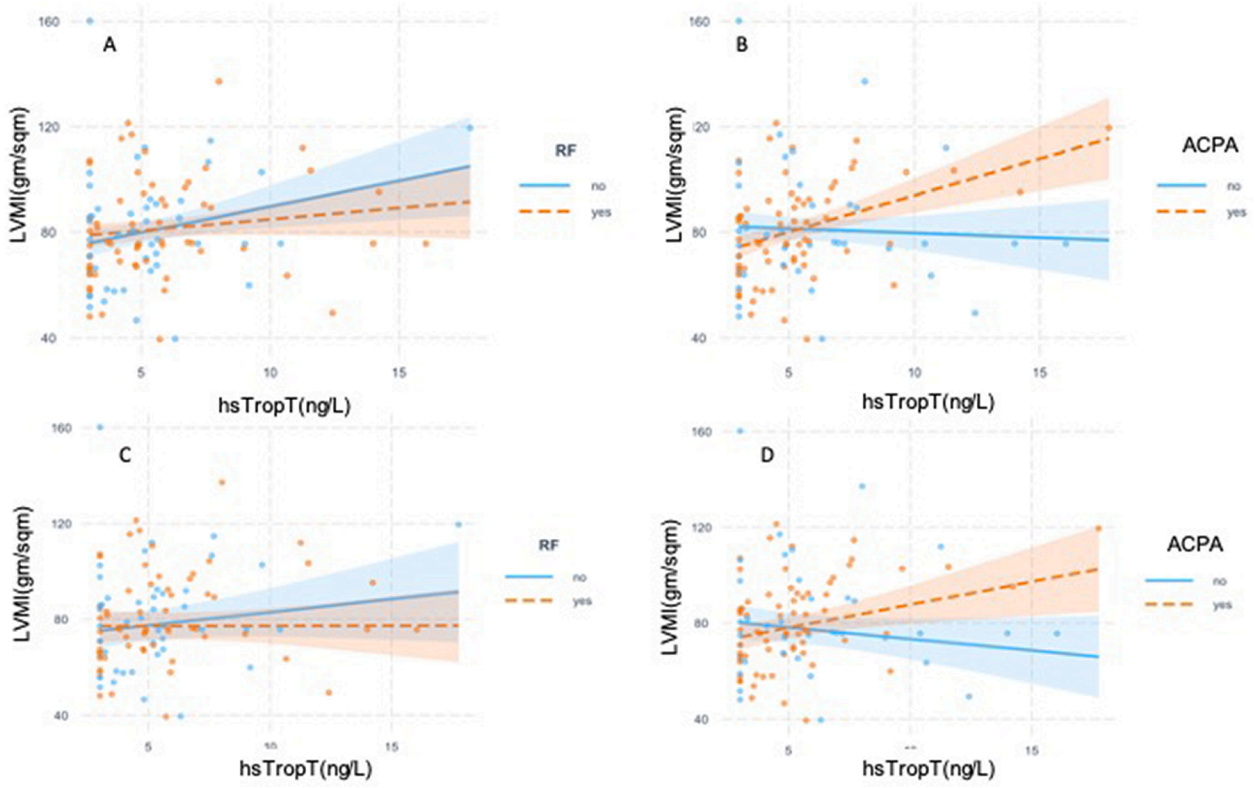

Fig. 1. Interaction between hsTropT and LVMI stratified by rheumatoid biomarkers in rheumatoid arthritis patients without clinically overt cardiovascular diseases (A, B). Adjusted multivariate analysis (C, D). hsTropT, high-sensitivity troponin T; RF, rheumatoid factor; LVMI, left ventricular mass index; ACPA, anti-cyclic citrullinated peptide antibody.

There were no statically significant differences of cardiac anatomy and function among four groups of either positive or negative RF and ACPA biomarkers in patients without clinical overt cardiovascular disease (Table 5) Patients with positive both RF and ACPA were more likely to have higher LVMI than those in other groups. Slightly higher LVEF, but slightly lower E/e', in patients with negative both RF and ACPA was found comparing to those with positive at least one biomarker.

The interaction effect between hsTropT and rheumatoid biomarkers (RF and ACPA) on cardiac anatomy (LVMI) and function (E/e') is shown in Figs. 1 and 2, respectively. Univariate (Fig. 2B) and multivariate analyses (Fig. 2D) revealed that the effect of hsTropT on LVMI was enhanced by the presence of ACPA. As illustrated by the graphs in Figs. 1 and 2, the slope for the ACPA-positive group was steeper than that for the ACPA-negative group, and there was no interaction effect between hsTropT and rheumatoid biomarkers on E/e'.

The final models show the relationships of LVMI and E/e' with significant variables adjusted with cardiac and rheumatoid biomarkers including the interaction between hsTropT and rheumatoid biomarkers, are presented in Table 6. LVMI was significantly increased when the SBP was higher (adjusted β coefficient = 0.292, p = 0.036) and the NSAID was used (adjusted β coefficient = 8.681, p = 0.045). Only age was shown to be significant; in particular, as age increased, E/e' increased (adjusted β coefficient = 0.101, p = 0.009). The effects of cardiac and rheumatoid biomarkers and the interaction on LVMI and E/e' were not found.

4. Discussion

The hsTropT and NT-proBNP showed a weak correlation with cardiac anatomy and function in RA patients without clinically overt cardiovascular diseases. However, the RA patients, who had higher systolic blood pressure, used NSAID, or had positive ACPA with higher hsTropT levels, had probably higher risk of LVMI which will guide the clinicians to pay attention on clinical observation and cardiac biomarkers in RA patients before clinically overt cardiac diseases are presented. Moreover, the cardiac function was also needed to be monitored in older RA

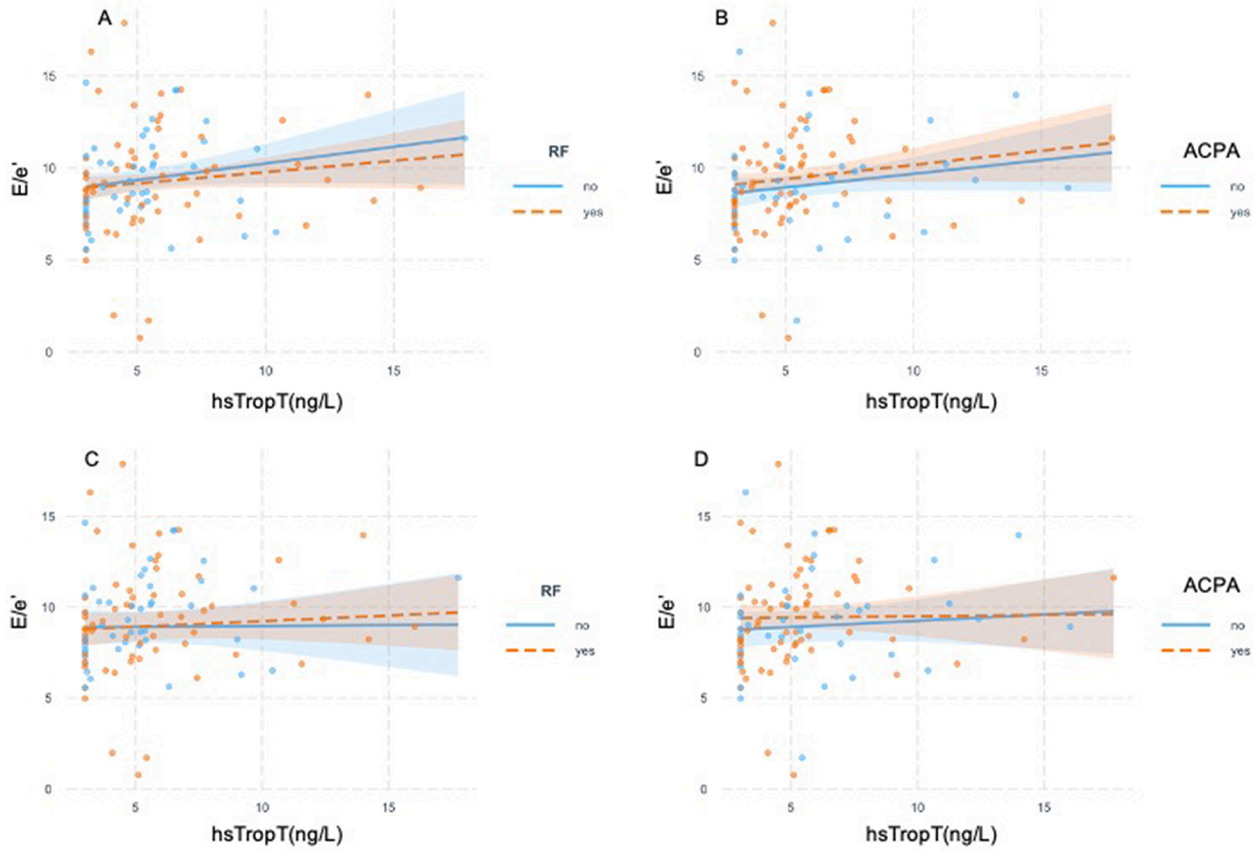

Fig. 2. Associations between hsTropT and E/e' stratified by rheumatoid biomarkers (A, B) in rheumatoid arthritis patients without clinical overt cardiovascular diseases. Adjusted multivariate analysis (C, D). hsTropT, high-sensitivity troponin T; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; E/e', early filling velocity on transmitral Doppler and early relaxation velocity on tissue Doppler.

Table 6
Multivariate analysis of LVMI and E/e' ratio.

Factors	LVMI			E/e'		
	Adjusted β coefficient	95% CI of β coefficient	p value	Adjusted β coefficient	95% CI of β coefficient	p value
Intercept	45.497	5.149, 85.845	0.028	3.557	−1.014, 8.128	0.126
hsTropT	−0.931	−4.318, 2.456	0.587	0.070	−0.403, 0.543	0.769
NT-proBNP	−0.013	−0.073, 0.047	0.669	−0.003	−0.011, 0.005	0.491
RF	−0.308	−18.977, 18.362	0.974	−0.040	−2.606, 0.526	0.976
ACPA	−15.556	−34.533, 3.420	0.107	0.580	−2.019, 3.180	0.659
SBP	0.292	0.019, 0.565	0.036	-	-	-
NSAID	8.681	0.184, 17.178	0.045	-	-	-
Age	-	-	-	0.101	0.026, 0.176	0.009
Interaction						
hsTropT *RF +	0.437	−2.776, 3.651	0.788	0.016	−0.427, 0.458	0.944
hsTropT *ACPA +	2.839	−0.338, 6.017	0.079	−0.037	−0.470, 0.397	0.867

+, positive; LVMI, left ventricular mass index; E/e', early filling velocity on transmitral Doppler and early relaxation velocity on tissue Doppler; hsTropT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; SBP, systolic blood pressure; NSAID, non-steroidal anti-inflammatory drug.

patients due to the fact that higher E/e' ratio was increased by patients' age.

It was not surprising to find that hsTropT and NT-proBNP were weakly correlated with cardiac anatomy and function in our study because the RA patients had no clinically overt cardiovascular diseases. However, the hsTropT and NT-proBNP levels detected in the study population were slightly higher than those found in the general population [39,40]. This supports some probable mechanisms of cardiac marker alterations in RA patients. According to previous reviews in the literature, hsTropT and NT-proBNP are nonspecific markers of cardiac abnormalities [41,42], and their excretion may be affected by biological variation [43,44].

hsTropT was correlated with cardiac structure and function to a greater extent than NT-proBNP. This may be explained by the findings of a previous study in which hsTropT was related to an abnormal myocardium, irrespective of causative factors, whereas NT-proBNP was mostly related to the compensatory cardiac ventricular response to pressure and volume overload [45]. In addition, a previous study showed that patients with high LVMI had low capillary density and high LV mass, which were related to microvascular dysfunction, resulting in an ischemic myocardium and the release of hsTropT [15]. To date, only 1 study has confirmed the relationship between hsTropT and LVMI in RA

patients [46]; nonetheless, it did not account for the effect of biomarkers in RA patients.

The results of our study indicated a higher LVMI in RA patients in the presence of ACPA and RF; however, the difference was not significant, which may be attributable to the small sample size. The high LVMI in RA patients, which was similar to the findings of an increasing LVMI in predialytic chronic kidney disease patients in previous studies [47,48] may be explained by a shared mechanism of the relationship of chronic systemic inflammation in RA patients and in chronic kidney disease patients. Moreover, the indolent ischemia in RA may contribute to cardiac remodeling, resulting in an increased LVMI [20,49].

In the present study, the effect of hsTropT on LVMI was probably modified by the presence of ACPA in RA patients without clinically overt cardiovascular diseases since it was significant in univariate, not multivariate analysis. Of note, no previous studies have taken this effect modifier into account. This interaction effect of ACPA on the relationship between hsTropT and LVMI can be mediated by the immune complex between ACPA and citrullinated proteins, including vimentin, enolase, and fibronectin, which can cause inflammation in the rheumatoid synovium and myocardial tissue [50]. An *in vitro* study observed strong citrullination staining in the myocardial interstitium of RA patients [51]. Higher ACPA was also associated with the presence of citrullinated protein within atherosclerotic plaques, which may play a role in the large atherosclerotic burden, leading to the impaired resolution of inflammation within the atherosclerotic plaque [52]. Increased SBP and NSAID use were related to increased LVMI could be explained by the SBP was modified left ventricular mass [53] with confirm by the high prevalence of left ventricular hypertrophy [54] and NSAIDs enhanced the effect of angiotension II [55] with causing abnormal finding on echocardiography [56].

In our study, cardiac and rheumatoid biomarkers showed no significant association with E/e'. This may be because E/e' reflects cardiac function in specific clinical symptoms of heart failure [57]. Only age was identified to be significant; in particular, as age increased, E/e' increased, which was consistent with the findings of a previous study that included healthy volunteers [58]. The effect of age can be explained by the enhanced intrinsic inflammation and inadequate resolution of inflammation [59,60]. The identification of the modifying effect of cardiac and rheumatoid biomarkers, particularly hsTropT and ACPA, on LVMI suggested a link between the basic pathophysiology of ACPA-related inflammation and indolent myocardial ischemia with LVMI-related RA.

This study had some limitations. First, our cross-sectional design could not represent the causal relationship between biomarkers and cardiac anatomy and function; however, we included RA patients without clinically overt cardiovascular diseases who were less likely to have pathological cardiovascular diseases. Second, both RF and ACPA were recorded as positive or negative; therefore, the correlation tests for their levels were limited. Third, only 7 parameters of cardiac anatomy and 7 parameters of cardiac function were selected for use in this study, and only 1 parameter for each of anatomy and function was chosen. Fourth, the majority of patients analyzed were female, thus these biomarker findings may be limited to female patients. However, this disease was common in female so this limitation might be minimal. Fifth, the explicit information on history of alcohol consumption was not recorded even all patients said they did not drink alcohol. The bias of this information ascertainment may be minimal since the majority of RA patients were female who were less likely to have alcohol consumption. Finally, the findings of this study cannot be generalized to RA patients with clinical cardiovascular diseases.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Duangkamol Aiewruengsurata reports financial support was provided by Prince of Songkla University. Thanapon Nilmoje reports a relationship with Prince of Songkla University that includes: funding grants.

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