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(Citation)
International Journal of Cardiovascular Imaging,37(1):197-205

(Issue Date)
2021-01

(Resource Type)
journal article

(Version)
Accepted Manuscript

Association between clinical risk factors and left ventricular function in patients with breast cancer following chemotherapy

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Abstract

Purpose: The sequential or concurrent use of two different types of agents such as anthracyclines and trastuzumab may increase myocardial injury and cancer therapeutics-related cardiac dysfunction (CTRCD), which is often the result of the combined detrimental effect of the two therapies for breast cancer patients. However, the association between clinical risk factors and left ventricular (LV) function in such patients is currently unclear.

Methods: We studied 86 breast cancer patients with preserved LV ejection fraction (LVEF) and treated with anthracyclines, trastuzumab, or both. Echocardiography was performed before and 16 days after chemotherapy. In accordance with the current position paper, clinical risk factors for CTRCD were defined as: cumulative dose of doxorubicin > 240 mg/m^2, age > 65-year-old, body mass index > 30 kg/m^2, previous radiation therapy, B-type natriuretic peptide > 100 pg/mL, previous history of cardiovascular disease, atrial fibrillation, hypertension, diabetes, and smoking.

Results: The relative decrease in LVEF after chemotherapy for patients with more than four risk factors was significantly greater than that for patients without (-9.3±10.8% vs. -2.2±10.2%; p=0.02). However, this finding did not apply to patients with more than one, two or three risk factors. Patients with more than four risk factors also tended to show a higher prevalence of CTRCD than those without (14.3% vs. 2.8%; p=0.12). Moreover, the relative decrease in LVEF became greater as the number of risk factors increased.

Conclusions: This study found multiple risk factors were associated with LV dysfunction following chemotherapy. Our findings can thus be expected to have clinical implications for better management of patients with breast cancer referred for chemotherapy.

Key words: Echocardiography, cancer therapeutics-related cardiac dysfunction, risk factors

Introduction

Advances in treatment have led to improved survival of cancer patients, but have also increased morbidity and mortality due to treatment side effects [1, 2]. Cardiovascular diseases are some of the most frequent of these side effects, and there is a growing concern that they may lead to premature morbidity and death among cancer survivors [3]. This may be the result of cardiotoxicity, which involves direct effects of the cancer treatment on left ventricular (LV) function and structure or may be due to accelerated development of cardiovascular diseases. Notably, the mortality rate for patients with cancer therapeutics-related cardiac dysfunction (CTRCD) is reportedly as high as 60% by 2 years after treatment [4]. However, if CTRCD is detected early and treated with heart failure (HF) medications, patients frequently have a good functional recovery [5]. Thus, early detection of CTRCD is essential for avoiding or delaying progression to HF in patients with a history of using cardiotoxins, but its assessment can be challenging.

For patients with breast cancer, the sequential or concurrent use of two different types of agents such as anthracyclines and trastuzumab may increase LV myocardial injury, while CTRCD is often the result of the combined detrimental effect of the two therapies. Furthermore, breast cancer was found to be the cumulative primary cause of death during the first 5 to 10 years following breast cancer diagnosis, whereas cardiovascular diseases became the cumulative primary cause of death during longer follow-ups [6]. For risk stratification to detect the development of CTRCD, the current position paper from the European Society of Cardiology (ESC) lists several factors associated with risk of cardiotoxicity following treatment with chemotherapy [2]. However, details of the association between these clinical risk factors for CTRCD and LV function in patients with breast cancer remain unclear. Accordingly, the aim of this study

was to investigate the impact of baseline risk factors on LV function in patients with preserved LV ejection fraction (LVEF) who have undergone anthracycline or trastuzumab chemotherapy for breast cancer.

Materials and Methods

Study population

We retrospectively enrolled 206 consecutive patients with breast cancer treated at Kobe University Hospital between June 2008 and May 2019. Excluded were patients with: (1) no administration of anthracyclines or trastuzumab; (2) no echocardiographic examination before or after anthracycline and trastuzumab chemotherapy; (3) LV systolic dysfunction before chemotherapy, defined as a LVEF < 50%. After exclusion of the above patients, the patient study group consisted of 86 patients with breast cancer. This study was approved by the local ethics committee of our institution in conformity with the Declaration of Helsinki (No. B190263).

Echocardiography

Echocardiographic studies were performed before and median 16 (1-61) days after completion of chemotherapy by using a commercially available echocardiography system (Aplio Artida, Aplio 400 and Xario; Canon Medical Systems, Tochigi, Japan, Vivid 7 and E9; GE-Vingmed, Horten, Norway, and iE33; Philips Medical Systems, Andover, MA). Digital routine grayscale two-dimensional cine loops from three consecutive heart beats were obtained at end-expiratory apnea from standard parasternal and apical views. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American

Society of Echocardiography (ASE) / European Association of Cardiovascular Imaging (EACVI) [7].

Speckle-tracking strain analysis was performed for each patient with the aid of a single dedicated software to evaluate LV longitudinal function, which was assessed in terms of global longitudinal strain (GLS) (AutoSTRAIN, TOMTEC-ARENA; TOMTEC Imaging Systems GmbH, Unterschleissheim, Germany). Briefly, apical 4-chamber, 2-chamber and long-axis views with the Digital Imaging and Communications in Medicine (DICOM) formatted file images were uploaded onto a personal computer for subsequent off-line GLS analysis. Longitudinal speckle-tracking strain was calculated by means of an automated contouring detection algorithm, and manual adjustments of regions of interest were performed where necessary. GLS was then determined as the averaged peak longitudinal strain of 18 LV segments, and was expressed as an absolute value in line with current guidelines [7].

Definition of CTRCD

In accordance with the current definition of CTRCD by ASE and ~~the~~ EACVI consensus statement, CTRCD was defined as a decline in LVEF of > 10% to an absolute value of < 53% after the termination of chemotherapy [8].

Definition of risk factors for CTRCD

The baseline risk factors for CTRCD were categorized, based on the current ESC position paper, as (1) a cumulative total doxorubicin dose of > 240 mg/m^2, (2) age > 65-year-old, (3) body mass index > 30 kg/m^2, (4) a previous history of radiation therapy to chest or mediastinum, (5) B-type natriuretic peptide > 100 pg/mL, (6) a previous history of cardiovascular disease, (7) atrial fibrillation, (8) hypertension, (9) diabetes mellitus, (10) current or ex-smoker [2].

Statistical analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data, and as the median and interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of subgroups were compared by means of the Student *t* test, Mann-Whitney U test, or paired samples *t* test as appropriate. Proportional differences were compared by means of Fisher's exact test, chi-squared test, or Mcnemar test as appropriate. Sequential logistic models for predicting CTRCD were constructed to determine any incremental benefits of using more than four risk factors compared with using only conventional baseline echocardiographic variables consisting of LVEF, mitral inflow E and mitral e' annular velocities ratio (E/e'), and mitral inflow E and A velocities ratio (E/A). A statistically significant increase in the global log-likelihood χ^2 of the model was defined as an increment in predictive value. The initial univariate logistic regression analysis to identify univariate determinants of developing CTRCD was followed by a multivariate logistic regression model using stepwise selection, with the p levels for entry from the model set at < 0.10. Optimal cutoff value for association of a cumulative total doxorubicin dose with LV dysfunction after chemotherapy were determined with receiver-operator characteristics curve analysis. P value < 0.05 was considered statistically significant for all tests. All the analyses were performed with commercially available software (MedCalc software version 19.1; MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

The baseline clinical and echocardiographic characteristics of the 86 patients with breast cancer are summarized in Table 1. Their mean age was 59±13 years, 85 (99%) were female, and LVEF was 66.5±4.7%.

Comparison of changes in LVEF of patients with and without risk factors

Figure 1 shows changes in LVEF of patients with and without risk factors. The relative decrease in LVEF was became greater as the number of risk factors increased, and the relative decrease in LVEF after chemotherapy of patients with more than four risk factors was significantly greater than that in patients without (-9.3±10.8% vs. -2.2±10.2%; p=0.02). However, this relationship was not observed between patients with more than one (-3.0±10.5% vs. -3.2±8.3%; p=0.97), two (-3.3±11.2% vs. -3.4±9.3%; p=0.96) or three risk factors (-5.3±11.3% vs. -1.9±9.6%; p=0.14) and those without. We did not examine the difference between patients with more than five risk factors and those without because of the very small number (only three) of patients with more than five risk factors. Moreover, patients with more than four risk factors tended to show a higher prevalence of CTRCD compared to those without (14.3% vs. 2.8%; p=0.12). The comparison of echocardiographic parameters between baseline and after completion of chemotherapy is shown in Table 2. After completion of chemotherapy, LVEF significantly decreased from 66.5±4.7% to 64.1±6.1% (p=0.002) and LV end-systolic volume significantly increased from 23.5 mL (19.0-27.7) to 24.0 mL (20.0-27.6) (p=0.02). In addition, the comparison of clinical and echocardiographic characteristics of patients with and without CTRCD are summarized in Table 3. Though small number of patients with CTRCD, patients with CTRCD were more likely to be smoker (p=0.003), and tended to be higher total cumulative doxorubicin dose (p=0.08) and higher LV mass index (p=0.07) compared to those without CTRCD.

Associated factors for CTRCD

Table 4 shows the results of the univariate and multiple regression analysis of associated factors for developing CTRCD. LV mass index and more than four risk factors were entered to multiple regression analysis from univariate regression analysis, but none of them were independent parameters. The incremental benefits of using sequential logistic models for the prediction of CTRCD after chemotherapy are shown in Figure 2. LVEF, E/A and E/e' were chosen as baseline sequential models because of common global LV function. A model based on baseline conventional echocardiographic variables including LVEF, E/e', and E/A (χ^2=0.8) was significantly improved by the addition of the variable of having more than four risk factors (χ^2=5.9; p=0.02). Similarly, the addition of baseline GLS tended to result in improvement (χ^2=2.7; p=0.17).

Comparison of echocardiographic parameters for patients with more than any of four risk factors and those without

Echocardiographic parameters between patients with more than any of four risk factors and those without are shown in Table 5. Patients with more than four risk factors were more likely to have LV hypertrophy (interventricular septal thickness end-diastole: 10.3±2.1 mm vs. 9.0±1.9 mm; p=0.04, posterior wall thickness end-diastole: 10.4±1.7 mm vs. 9.3±1.7 mm; p=0.02, LV mass index: 109.3±29.0 g/m^2 vs. 83.2±21.0 g/m^2; p<0.001), and larger left atrial volume index (36.3±11.4 mL/m^2 vs. 29.6±10.1 mL/m^2; p=0.03). Furthermore, GLS tended to be lower (18.4±2.8% vs. 20.0±2.6%; p=0.06) and E/e' tended to be higher (10.4 [8.9-13.0] vs. 9.0 [7.4-10.9]; p=0.06) for patients with more than four risk factors compared to those without.

Optimal cut off value of a cumulative total doxorubicin dose for predicting LV dysfunction for patients with more than any of four risk factors and those without

LV dysfunction after completion of chemotherapy was determined as relative decrease of LVEF > 5% in this study. An optimal cut off value of a cumulative total doxorubicin dose for predicting LV dysfunction, determined by means of receiver-operator characteristics curve analysis, in patients with more than any of four risk factors was lower than that in those without (> 180 mg/m^2 vs. > 280 mg/m^2).

Discussion

The findings of our study demonstrate that there was an association between treatment with anthracyclines, trastuzumab, or both, of patients with breast cancer and the development of LV dysfunction following chemotherapy. This association became stronger with an increase in the number of risk factors, and was especially strong for patients treated with chemotherapy who had more than four risk factors. In addition, this finding can affect an optimal cut off value of a cumulative total doxorubicin dose for predicting LV dysfunction.

Risk stratification for subsequent LV dysfunction after chemotherapy

Current advances in various cancer treatment have resulted in significant improvement in cancer-specific survival. In addition, mortality rates for breast cancer, as for other cancers, have also declined. The survival of breast cancer patients depends on many factors, including age at diagnosis, tumor stage, tumor grade, estrogen receptor status, progesterone receptor status, socioeconomic factors and other non-cancer related clinical conditions such as preexisting health status, functional status and social connections [9, 10]. Elderly patient with breast cancer in particular have been evidenced as a significantly greater risk of cardiac dysfunction after chemotherapy [11-13]. This finding does not apply only to breast cancer, however. Survivors of various other cancers

are increasingly subject to some cardiovascular diseases related to chemotherapies, compounded by the development or progression of age-related cardiovascular risk factors with prolonged survival. The proportional distribution of cumulative causes of death for all cancer patients depends on the length of follow-up time. In the first 5 to 10 years following breast cancer diagnosis, breast cancer was found to be the cumulative primary cause of death, whereas cardiovascular diseases became the cumulative primary cause of death with longer follow-ups [6]. Among these diseases, cardiovascular toxicity remains a devastating complication of cancer treatment. The mortality rate for patients with CTRCD is as high as 60% by 2 years after treatment, representing a 3.5-fold greater hazard when compared with patients with idiopathic dilated cardiomyopathy [4]. Despite their well-documented cardiotoxicity, predominantly evidenced by LV dysfunction, anthracyclines remain the preferred agents for a wide variety of malignancies including breast cancer. The addition of trastuzumab, a monoclonal antibody directed against human epidermal growth factor receptor 2, to standard adjuvant chemotherapy significantly improves disease-free and overall survival in the 20-30% of patients with breast cancer who overexpress this proto-oncogene [14]. However, trastuzumab is also cardiotoxic, resulting in cardiac dysfunction in 3-5% of patients [14]. For patients with breast cancer, therefore, the sequential or concurrent use of two different types of agents such as anthracyclines and trastuzumab may increase myocardial injury and CTRCD is often the result of the combined detrimental effect of the two therapies.

Although early detection of CTRCD is essential for delaying progression to HF, risk stratification for the development of CTRCD before chemotherapy can be difficult. The current position paper from the ESC lists several pre-chemotherapy risk factors for the development of CTRCD. In addition, we could show that there is an association

between patients with breast cancer and the development of LV dysfunction following chemotherapy. This association became stronger as the number of risk factors increased and was especially strong for patients with more than four risk factors.

Clinical implications

Risk stratification for the development of CTRCD appears to hold promise for delaying progression to HF for cancer patients with preserved LVEF who are scheduled to undergo chemotherapy. There has been a growing interest in early detection of CTRCD by means of GLS, because it is a more sensitive and robust parameter for detecting subclinical LV dysfunction than other conventional LV functional parameters [2, 8, 15-18]. Specifically, the current position paper from the ESC states that a ≥ 15% early reduction in GLS during chemotherapy appears to be the most useful parameter for the prediction of cardiotoxicity, and possibly of risk of CTRCD [2]. Moreover, our group recently reported that baseline GLS was found to be associated with LV dysfunction after anthracycline chemotherapy and the development of HF during long-term follow-up of patients with malignant lymphoma and preserved LVEF [19]. Although GLS is an increasingly widely accepted perceptive parameter, it is still not a routine echocardiographic parameter in many institutions, and a number of oncologists may not familiar with it. When this technology may therefore not be available, assessment of the aforementioned clinical risk factors for the prediction of cardiotoxicity is simple and easy to use and could be useful for predicting LV dysfunction following chemotherapy. Thus, watchful observation during and after chemotherapy or early preventive strategies with established cardioprotective medications such as angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and beta-blockers may be advisable for patients with breast cancer and preserved LVEF and with the multiple risk factors detailed

in the current study report. In addition, a cumulative total doxorubicin dose is thought to be an important risk factor among the baseline risk factors for CTRCD. Our study showed the different cutoff value between patients with more than any of four risk factors and those without. Our finding suggested that even lower cumulative total doxorubicin dose can develop LV dysfunction in patients with more than any of four risk factors. Thus, attending physicians should take particular care to a cumulative total doxorubicin dose for avoid the development of CTRCD in patients with more than any of four risk factors.

Study limitations

This study comprised a small number of patients and was a single-center retrospective study, so that future prospective studies with larger patient populations will be needed to validate our findings. In addition, each risk factor was assumed to be equivalent in this study, but may in fact differ in the ability to predict the development of CTRCD.

Conclusions

This study found that breast cancer and multiple clinical risk factors were associated with LV dysfunction following chemotherapy. Our findings can thus be expected to have clinical implications for better management of patients with breast cancer referred for chemotherapy.

Compliance with Ethical Standards

Conflict of interest:

Kentaro Yamashita declares that he has no conflict of interest. Hidekazu Tanaka declares that he has no conflict of interest. Keiko Hatazawa declares that he has no

conflict of interest. Yusuke Tanaka declares that he has no conflict of interest. Keiko Sumimoto declares that he has no conflict of interest. Ayu Shono declares that he has no conflict of interest. Makiko Suzuki declares that he has no conflict of interest. Shun Yokota declares that he has no conflict of interest. Makiko Suto declares that he has no conflict of interest. Jun Mukai declares that he has no conflict of interest. Hiroki Takada declares that he has no conflict of interest. Kensuke Matsumo declares that he has no conflict of interest. Hironobu Minami declares that he has no conflict of interest. Ken-ichi Hirata declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Figure Legends

Figure 1: Bar graphs showing comparisons of the relative decrease in LVEF after chemotherapy for patients with and without risk factors. The relative decrease for patients with more than four risk factors was significantly higher than that for patients without, but this relationship was not observed between patients with more than one, two or three risk factors and those without.

Figure 2: The incremental benefits of using sequential logistic models for the prediction of CTRCD after chemotherapy, show that a model based on baseline conventional echocardiographic variables including LVEF, E/e', and E/A was significantly improved by the addition of the variable of having more than four risk factors. The addition of baseline GLS tended to result in similar improvement.

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Table 1

Demographic and clinical characteristics of patients with breast cancer

	Patients (n=86)
Clinical Data	
Age, years	58.8±13.1
Gender (female), n (%)	85 (99)
Body mass index, kg/m^2	22.9±3.9
B-type natriuretic peptide, pg/mL	36.8 (16.7-58.4)
Comorbidity, n (%)	
Hypertension	27 (31)
Diabetes mellitus	5 (6)
Smoking	22 (26)
Atrial fibrillation	2 (2)
Previous history of cardiovascular disease	9 (10)
Therapy for breast cancer, n (%)	
Anthracycline-based therapy, n (%)	61 (71)
Cumulative doxorubicin dose (mg/m^2)	240 (0-240)
Trastuzumab-based therapy, n (%)	55 (64)
Combined therapy with anthracycline and trastuzumab, n (%)	32 (37)
Radiation therapy, n (%)	39 (45)
Echocardiographic parameters	
LV end-diastolic diameter, mm	42.6±4.3
LV end-systolic diameter, mm	26.5±3.3
IVSTd, mm	9.2±2.0
PWTd, mm	9.5±1.7
LV mass index, g/m^2	87.5±24.3
LV end-diastolic volume, mL	70.0 (59.0-79.8)
LV end-systolic volume, mL	23.5 (19.0-27.7)
LVEF, %	66.5±4.7
Left atrial volume index, mL/m^2	30.9±10.7
E/A	0.89 (0.75-1.23)
E/e’	9.2 (7.7-11.1)
TR-PG, mmHg	20.7±6.2
Global longitudinal strain, %	19.6±2.8

Aortic stenosis, n (%)	
Mild	1 (1)
Moderate	0 (0)
Severe	0 (0)
Aortic regurgitation, n (%)	
Mild	13 (15)
Moderate	0 (0)
Severe	0 (0)
Mitral stenosis, n (%)	0 (0)
Mitral regurgitation, n (%)	
Mild	15 (17)
Moderate	0 (0)
Severe	0 (0)
Tricuspid regurgitation, n (%)	
Mild	26 (30)
Moderate	2 (2)
Severe	0 (0)
Cardiovascular Medications, n (%)	
ACEIs/ARBs	15 (17)
Beta-blockers	4 (5)
Mineralocorticoid receptor antagonists	1 (1)

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

LV=left ventricular; IVSTd=interventricular septal thickness end-diastole; PWTd=posterior wall thickness end-diastole; E=peak early diastolic mitral flow velocity; A=peak late diastolic mitral flow velocity; e'=spectral pulsed-wave Doppler-derived early diastolic velocity from the septal mitral annulus; TR-PG=tricuspid regurgitation pressure gradient; ACEI=angiotensin converting-enzyme inhibitor; ARB=angiotensin receptor blocker

Table 2

Comparison of echocardiographic parameters between baseline and after completion of chemotherapy

	Baseline	After completion of chemotherapy	P value
LV end-diastolic volume, mL	70.0 (59.0-79.8)	66.4 (58.0-81.1)	0.58
LV end-systolic volume, mL	23.5 (19.0-27.7)	24.0 (20.0-27.6)	0.02
LVEF, %	66.5±4.7	64.1±6.1	0.002
LV mass index, g/m^2	87.5±24.3	85.5±19.3	0.35
Left atrial volume index, mL/m^2	30.9±10.7	30.2±9.7	0.76
Moderate or severe aortic stenosis, n (%)	0 (0)	0 (0)	-
Moderate or severe aortic regurgitation, n (%)	0 (0)	0 (0)	-
Moderate or severe mitral regurgitation, n (%)	0 (0)	2 (2)	0.50
Moderate or severe tricuspid regurgitation, n (%)	2 (2)	5 (6)	0.38

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data.

Abbreviation as in Table 1

Table 3

Comparison of clinical and echocardiographic characteristics of patients with and without CTRCD

	Patients **with** CTRCD (n=4)	Patients **without** CTRCD (n=82)	P value
Clinical Data			
Age, years	54.3±12.8	59.0±13.2	0.48
Gender (female), n (%)	4 (100)	81 (99)	1.00
Body mass index, kg/m^2	21.5±2.2	23.0±4.0	0.45
B-type natriuretic peptide, pg/mL	15.7 (11.7-35.6)	36.8 (16.7-58.4)	0.28
Comorbidity, n (%)			
Hypertension	1 (25)	26 (32)	1.00
Diabetes mellitus	0 (0)	5 (6)	1.00
Smoking	4 (100)	18 (22)	0.003
Atrial fibrillation	0 (0)	2 (2)	1.00
Previous history of cardiovascular disease	1 (25)	8 (10)	0.37
Therapy for breast cancer, n (%)			
Anthracycline-based therapy	4 (100)	57 (70)	0.32
Cumulative doxorubicin dose, (mg/m^2)	240 (240-315)	240 (0-240)	0.08
Trastuzumab-based therapy	3 (75)	50 (61)	1.00
Radiation therapy	2 (50)	37 (45)	1.00
Echocardiographic parameters			
LV end-diastolic volume, mL	72.9 (67.0-83.4)	68.0 (55.5-76.4)	0.32
LV end-systolic volume, mL	24.9 (22.5-28.2)	21.7 (18.0-26.6)	0.39
LVEF, %	65.3±2.4	66.6±4.8	0.60
IVSTd, mm	9.3±1.4	9.2±2.0	0.95
PWTd, mm	9.0±1.6	9.5±1.7	0.53
LV mass index, g/m^2	109.2±31.7	86.4±23.6	0.07
Left atrial volume index, mL/m^2	35.6±7.4	30.6±10.8	0.37
E/e’	9.9 (8.0-11.1)	9.2 (7.7-11.1)	0.96
TR-PG, mmHg	18.8±4.6	20.5±6.6	0.65
Global longitudinal strain, %	19.0±3.4	19.6±2.7	0.69

Values are mean ± SD for normally distributed data and median and interquartile range

for non-normally distributed data.
Abbreviation as in Table 1

Table 4

Univariate and multiple regression analysis of associated factors for developing CTRCD

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Use of Trastuzumab	1.86	0.19-18.68	0.60			
LVEF	0.94	0.74-1.19	0.59			
LV mass index	1.03	1.00-1.06	0.09	1.02	0.98-1.06	0.29
Left atrial volume index	1.03	0.96-1.11	0.38			
E/A	1.94	0.35-10.71	0.45			
E/e’	0.95	0.70-1.29	0.72			
TR-PG	0.95	0.78-1.17	0.65			
Global longitudinal strain	1.08	0.75-1.56	0.69			
Risk factors ≥ 4	5.83	0.75-45.47	0.09	3.37	0.33-34.10	0.30

OR odds ratio, CI confidential interval

Other abbreviation as in Table 1

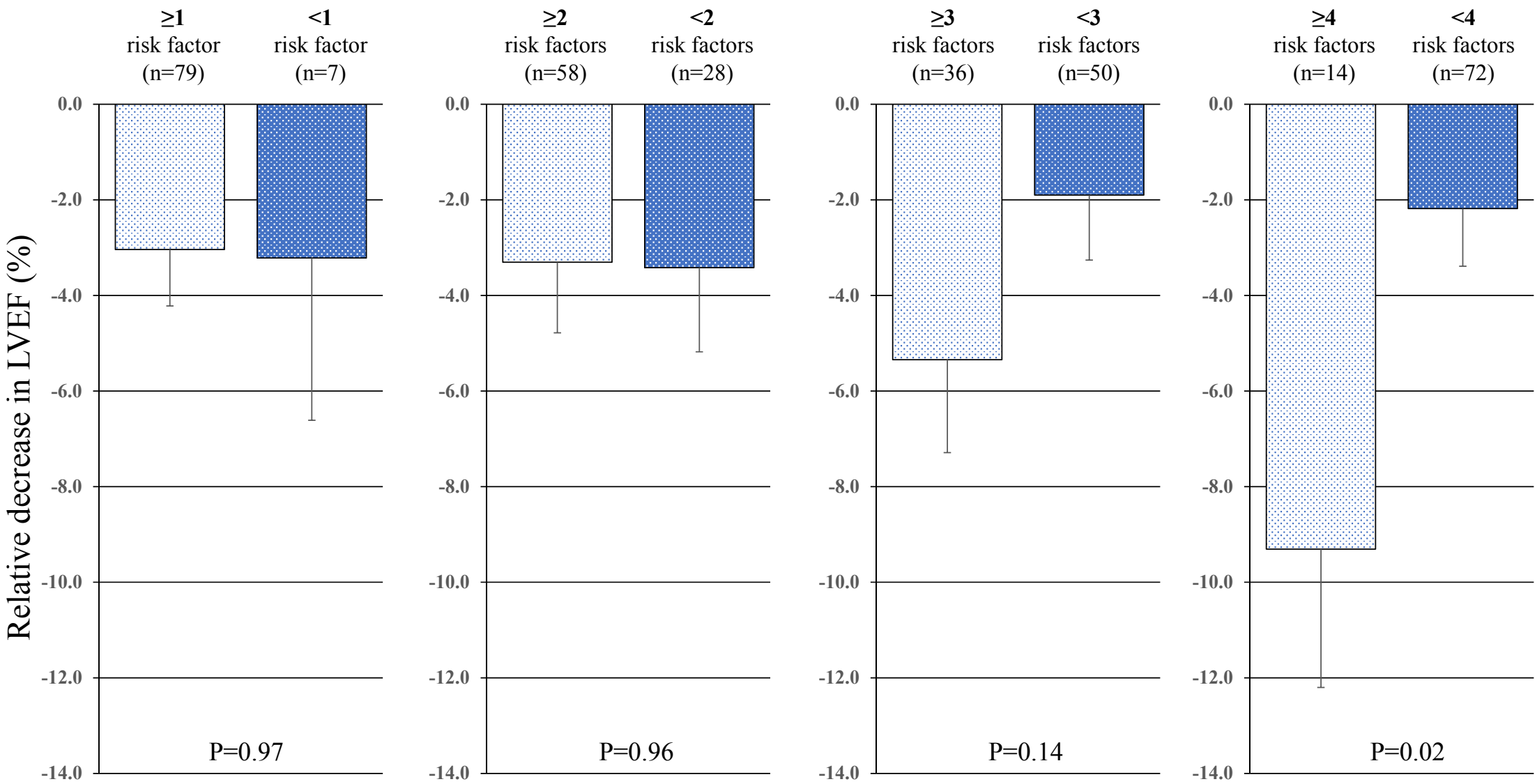
Table 5

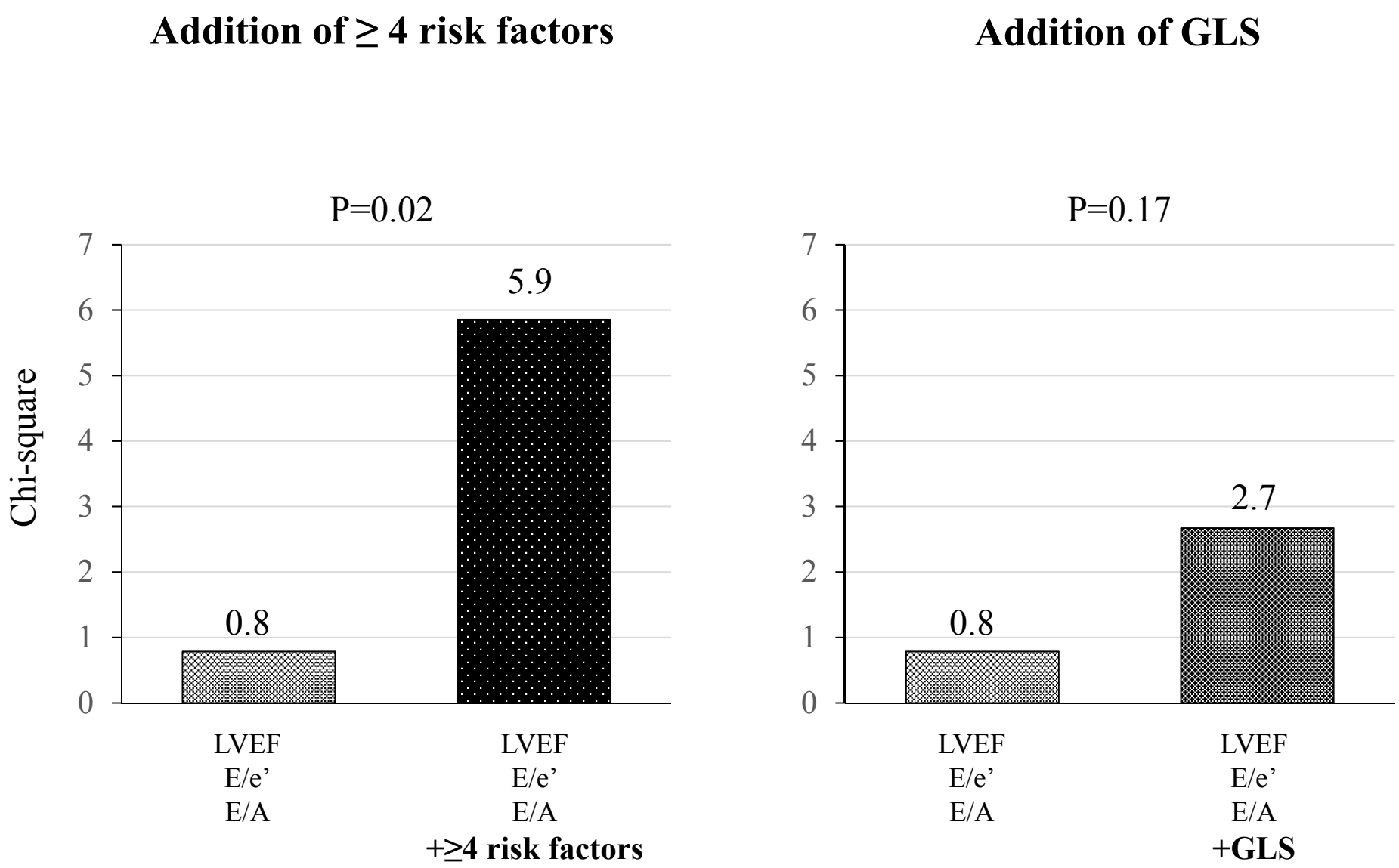
Comparison of echocardiographic parameters between patients with and without more than any of four risk factors

	≥4 risk factors (n=14)	<4 risk factors (n=72)	P value
LV end-diastolic volume, mL	63.2 (53.0-87.7)	70.3 (59.0-78.8)	0.66
LV end-systolic volume, mL	19.7 (15.3-28.5)	23.9 (19.8-27.4)	0.38
LVEF, %	67.8±4.6	66.3±4.7	0.27
IVSTd, mm	10.3±2.1	9.0±1.9	0.04
PWTd, mm	10.4±1.7	9.3±1.7	0.02
LV mass index, g/m^2	109.3±29.0	83.2±21.0	<0.001
Left atrial volume index, mL/m^2	36.3±11.4	29.6±10.1	0.03
E/e’	10.4 (8.9-13.0)	9.0 (7.4-10.9)	0.06
TR-PG, mmHg	24.4±9.5	19.9±5.8	0.08
Global longitudinal strain, %	18.4±2.8	20.0±2.6	0.06

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data.

Abbreviation as in Table 1


≥1 risk factor (n=79)
<1 risk factor (n=7)
≥2 risk factors (n=58)
<2 risk factors (n=28)
≥3 risk factors (n=36)
<3 risk factors (n=50)
≥4 risk factors (n=14)
<4 risk factors (n=72)
Relative decrease in LVEF (%)
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-14.0
P=0.97
P=0.96
P=0.14
P=0.02


Addition of ≥ 4 risk factors
P=0.02
Chi-square
7
6
5
4
3
2
1
0
0.8
5.9
LVEF
E/e'
E/A
LVEF
E/e'
E/A
+≥4 risk factors
Addition of GLS
P=0.17
7
6
5
4
3
2
1
0
0.8
2.7
LVEF
E/e'
E/A
LVEF
E/e'
E/A
+GLS