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Research paper

The usefulness of C-reactive protein to predict improving left ventricular function after aortic valve replacement in patients with aortic regurgitation

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ABSTRACT

Background: We aimed to clarify the predictive factors for left ventricular (LV) function after aortic valve replacement (AVR) in patients with aortic regurgitation (AR).

Methods and results: Among 555 patients who underwent AVR at our institution from January 2015 to December 2020, we enrolled 44 patients for whom only AVR (or AVR + aortic replacement) was performed. We defined LV dysfunction under any of the following criteria: LV ejection fraction (LVEF) <50 %, LV diastolic dimension >65 mm, LV systolic dimension (LVDs) >50 mm, or LVDs/body surface area > 25 mm/m2. Multivariable logistic regression analysis revealed high natural logarithm (ln) C-reactive protein (CRP) and low LVEF in the pre-AVR period significantly associated with LV dysfunction after AVR (ln CRP: odds ratio [OR] 4.15, 95 % confidence interval [CI] 1.44–11.98, $p < 0.01$; LVEF: OR 0.79, 95%CI 0.65–0.97, $p < 0.05$). Receiver-operating characteristic analysis revealed an area under curve of CRP and LVEF in the pre-AVR period for LV dysfunction after AVR of 0.84 and 0.83, respectively. Upon dividing the patients into four groups according to cutoff values of CRP (0.13 mg/dL) and LVEF (50 %) in the pre-AVR period, no patients (0/19) had LV dysfunction in the low CRP (<0.13 mg/dL) and high LVEF (≥50 %) group, and all patients (5/5) in the high CRP (≥0.13 mg/dL) and low LVEF (<50 %) group had LV dysfunction after AVR.

Conclusion: High CRP level was significantly and independently associated with LV dysfunction after AVR. Combination of CRP and LVEF values might be useful for predicting improvement in LV function after AVR.

1. Introduction

Chronic severe aortic regurgitation (AR) imposes significant volume and pressure overload on the left ventricle, resulting in compensatory but eventually detrimental structural changes in the myocardium [1,2]. Although such patients typically remain asymptomatic for a long time, the left ventricle is often dilated, and heart failure progresses despite successful aortic valve replacement (AVR) at the time of presentation of symptoms in AR patients [3,4]. Therefore, the American Heart Association and the European Society of Cardiology recommend aortic valve surgery in symptomatic or asymptomatic patients with depressed left ventricular (LV) systolic function or a significantly dilated left ventricle

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[5,6]. LV dysfunction in the preoperative period is widely known to be a useful prognostic marker for patients after AVR [4,7]. Therefore, preoperative LV function is an important issue for patients with AR. By contrast, Izumi et al. revealed that echocardiographic parameters at 1 year after AVR were more useful as predictive factors for long-term outcome than preoperative echocardiographic parameters in patients with AR [8]. Therefore, the predictive factors for LV dysfunction after AVR also seem to be important for AR patients. We previously reported that C-reactive protein (CRP), a representative biomarker of inflammatory factors, was important for LV dysfunction in patients with AR and concomitant collagen disease [9]. To our knowledge, however, there have been no reports about the association between CRP and LV dysfunction after AVR in all AR patients.

Against this backdrop, we performed a study to clarify the predictive factors for improvement of LV function after AVR in AR patients.

2. Methods

2.1. Study population

AVR was performed in 555 patients at Kumamoto University Hospital from January 2015 to December 2020. Of these patients, 441 had aortic stenosis (AS), 79 had AR, 25 had AS and AR, and 10 had prosthetic valve failure for surgical indication. Of these 79 patients in whom AVR was performed for AR, AVR only (or AVR + aortic replacement) was performed in 47 patients, dual valve surgery was performed in 20 patients, and AVR and coronary artery bypass grafting (CABG) were performed in 12 patients. For this study we selected the 47 patients who underwent only AVR (or AVR + aortic replacement). We then excluded one patient who had infective endocarditis and two patients who had no echocardiographic data in the follow-up period. Therefore, the final cohort comprised 44 patients who had moderate or severe AR in the pre AVR period (Fig. 1).

This study conformed to the principles outlined in the Declaration of Helsinki. It was approved by the institutional review board and ethics committees of Kumamoto University (No. 1588). The requirement for informed consent was waived because of the low-risk nature of this retrospective study and the inability to obtain consent directly from all patients. Instead, we extensively announced this study protocol at Kumamoto University Hospital and on our website (http://www2.kuh.kumamoto-u.ac.jp/tyuokensabu/index.html) and gave patients the opportunity to withdraw from the study.

2.2. Echocardiographic measurements

Transthoracic echocardiography (TTE) was performed in patients in a stable condition using the Vivid E95 or 7 (GE Vingmed, Horten, Norway), Aplio 500 (Toshiba, Tokyo, Japan), and Epiq 7G (Philips, Bothell, WA, USA) instruments, which were equipped with a 2.5-MHz phased-array transducer. The parasternal long-axis view, short-axis views at the basal, mid, and apical levels, and three standard apical views (four-chamber, two-chamber, and LV outflow long-axis) were acquired. Diastolic values of the interventricular septum thickness, posterior wall thickness, LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), and LV ejection fraction (LVEF) were measured according to the recommendations of the American Society for Echocardiography (ASE) [10]. The ratio of *E*-wave velocity to A-wave velocity of the pulsed-wave Doppler mitral flow image was calculated to quantify LV diastolic function. Peak velocity of early diastolic velocity (e' wave) of the septal mitral annulus was measured, and the ratio of E-wave velocity to e' was also calculated to quantify LV diastolic function [11]. The two-dimensional strain analysis was performed using a vendor-independent software program (2D Strain Analysis; TOMTEC Imaging Systems, Unterschleissheim, Germany). To assess the LV strain, the regional LS was calculated from the echocardiography images in the four-, three-, and two-chamber apical views. The regional LS was determined in 16 segments of the LV in accordance with the American Society for Echocardiography guidelines [10]. The LV global LS (LVGLS) was calculated as the average LS of these 16 segments. Valvular diseases were defined according to the 2017 ASE guideline [12]. The severity of AR was comprehensively assessed by using quantitative and qualitative methods according to the 2017 ASE guideline [12]. We clinically defined LV dysfunction if any of the following applied: LVEF <50 %, LV diastolic dimension >65 mm, LV systolic dimension (LVDs) >50 mm, or LVDs/

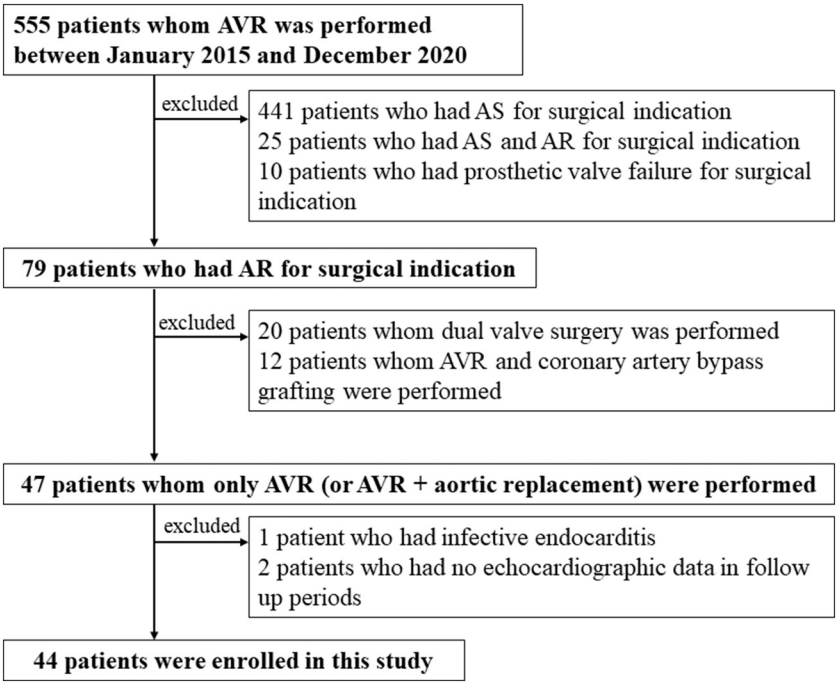

Fig. 1. Study flow chart detailing the inclusion and exclusion criteria for the study patients. AVR, aortic valve replacement; AS, aortic stenosis; AR, aortic regurgitation.

body surface area > 25 mm/m2, according to the American Heart Association 2014 guideline [5]. The effective orifice area (EOA) after AVR was calculated in accordance with the American Society for Echocardiography guidelines [13].

2.3. Data collection

Laboratory examination was performed 4 days (interquartile range [IQR], 2–5 days) before surgical AVR. Blood samples were collected early in the morning from fasted patients. Blood samples were stored at −80 °C before analysis of serum biochemical parameters. Echocardiography in the pre-AVR periods was performed 4 days (IQR, 2–10.5 days) before surgical AVR. Echocardiography in the follow-up periods was performed 365 days (IQR, 363–369 days) after surgical AVR. Echocardiographic findings and medications were ascertained by reviewing the medical records.

2.4. Definitions of clinical characteristics

Clinical characteristics were defined as follows. Body mass index was calculated as body weight/ (body height)2 (kg/m2). Hypertension was defined as the patient's self-report of a history of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or prior use of antihypertensive agents. Diabetes mellitus was defined as the patient's self-report of a history of hemoglobin A1c ≥6.5 % and fasting plasma glucose levels ≥126 mg/dL, or casual plasma glucose levels ≥140 mg/dL, and/or use of insulin or diabetes drugs. Dyslipidemia was identified by the patient's self-report of a history of antidyslipidemic drugs, low-density lipoprotein cholesterol levels ≥140 mg/dL, triglyceride levels ≥150 mg/dL, and/or high-density lipoprotein cholesterol levels <40 mg/dL. A bicuspid valve was identified by intraoperative findings. Ischemic heart disease was defined as prior history of myocardial infarction or percutaneous coronary intervention.

2.5. Timing of surgical intervention

The timing of surgical intervention for AR patients was decided by heart-team according to the recommendation of the American Heart Association and the European Society of Cardiology guideline [5,6].

2.6. Statistical analysis

We analyzed the time-dependent change in echocardiographic findings between the pre-AVR period and follow-up period by paired *t*-test. The clinical characteristics of patients between the LV dysfunction group and preserved LV function group in the follow-up period were compared by Student's *t*-test or the chi-squared test. Nonnormally distributed variables between these groups were compared by Mann-Whitney *U* test. Receiver-operating characteristic (ROC) analysis was performed to determine the cutoff values of CRP and LVEF in the pre-AVR period to predict LV dysfunction in the follow-up period. Decision curve analysis (DCA) was used to incorporate the clinical consequences of a decision into evaluations of diagnostic tests or prediction models [14]. Independent variables associated with LV dysfunction in the follow-up period were assessed by logistic regression analysis. The following variables were incorporated into the univariate logistic regression analysis model: age, male sex, body mass index, coronary risk factors (hypertension, diabetes mellitus, dyslipidemia), NYHA class, bicuspid valve, laboratory findings in the pre AVR period (B-type natriuretic peptide [BNP], CRP, estimated glomerular filtration rate, hemoglobin level), echocardiographic findings in the pre AVR period (left atrial volume index [LAVI], interventricular septal thickness in diastole, LV posterior wall thickness in diastole, LV end-diastolic diameter [LVDd], LV end-systolic diameter [LVDs], LVDs index, LVEF, LVGLS, E/e' ratio, severe AR), AVR only, biological valve, medication at discharge (angiotensin-converting enzyme inhibitor [ACEI]/angiotensin II receptor blocker [ARB], mineralocorticoid receptor antagonist [MRA], β-blocker), and echocardiographic findings in the follow-up period (EOA and mean transvalvular gradient). BNP and CRP were incorporated into univariate logistic regression analysis model after log transformation because these variables were nonnormally distributed variables. Variables with a p value of <0.05 were incorporated into the multivariable logistic regression analysis model. Statistical analyses were conducted with SPSS for Windows, version 24.0 (IBM, Armonk, NY, USA) and R program version 4.0.5 (package "PredictABEL", R Foundation, Vienna, Austria). Statistical significance was defined as $p <$ 0.05.

3. Results

3.1. Echocardiographic changes after AVR

We compared echocardiographic findings in the pre-AVR period with those in the follow-up period. In the pre-AVR period, 23 patients (52 %) had LV dysfunction and 21 (48 %) had preserved LV function. Sixteen patients of the LV dysfunction group in the pre-AVR period improved to reach the preserved LV function group in the follow-up period. By contrast, one patient from the preserved LV function group in the pre-AVR period worsened to LV dysfunction in the follow-up period. Finally, eight patients had LV dysfunction and 36 had preserved LV function in the follow-up period (Fig. 2). Table 1 shows the echocardiographic time-dependent change after AVR. LAVI, LVDd, LVDs, LVDs index, LVEDV, LVESV and tricuspid regurgitation velocity significantly decreased during the follow-up period compared with the pre-AVR period (LAVI, 37.0 ± 12.0 mm vs. 44.7 ± 12.8 mm, $p < 0.01$; LVDd, 44.9 ± 6.0 mm vs. 57.6 ± 7.5 mm, $p < 0.01$; LVDs, 29.5 ± 6.6 mm vs. 42.1 ± 8.7 mm, LVDs index 18.9 ± 4.2 vs. 26.8 ± 5.3 mm/m2, $p < 0.01$; LVEDV 76.1 ± 27.1 vs. 153.8 ± 64.9, $p < 0.01$; LVESV 32.9 ± 16.5 vs. 72.5 ± 35.0, $p < 0.01$; TRV, 2.18 ± 0.29 m/s vs. 2.30 ± 0.32 m/

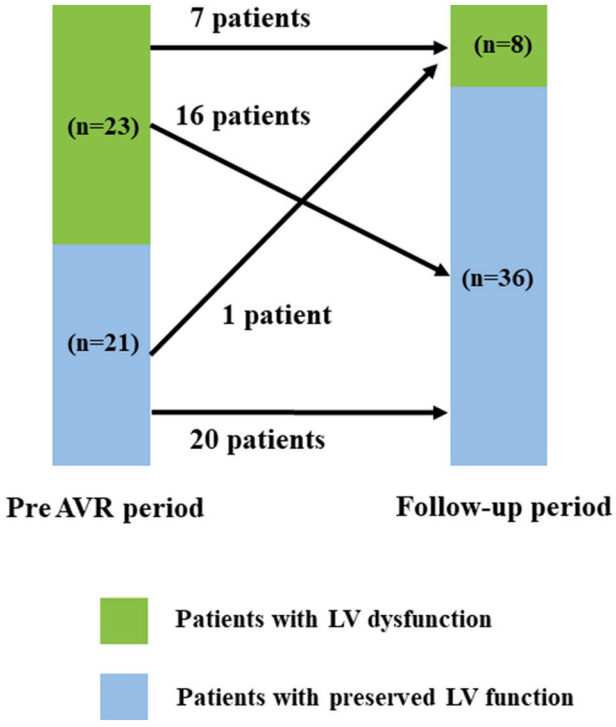

Fig. 2. Time-dependent change in the number of patients with LV dysfunction or those with preserved LV function. The LV function of 16 patients in the LV dysfunction group in the pre-AVR period improved up to the level of preserved LV function in the follow-up period. AVR, aortic valve replacement; LV, left ventricular.

Table 1
Echocardiographic time-dependent change after aortic valve replacement in patients with aortic valve regurgitation.

	Pre AVR period	Follow-up period	p value
LAVI (ml/m^2)	44.7 ± 12.8	37.0 ± 12.0	<0.01
LVDd (mm)	57.6 ± 7.5	44.9 ± 6.0	<0.01
LVDs (mm)	42.1 ± 8.7	29.5 ± 6.6	<0.01
LVDs index (mm/m^2)	26.8 ± 5.3	18.9 ± 4.2	<0.01
LVEDV (ml)	153.8 ± 64.9	76.1 ± 27.1	<0.01
LVESV (ml)	72.5 ± 35.0	32.9 ± 16.5	<0.01
LVEF (%)	55.6 ± 10.0	57.6 ± 6.8	0.08
LVGLS (%)	14.6 ± 3.8	14.8 ± 2.9	0.63
E/e' ratio	12.9 ± 6.4	11.1 ± 3.8	0.10
TRV (m/s)	2.30 ± 0.32	2.18 ± 0.29	<0.05

p value was evaluated by paired *t*-test.
Abbreviation, LAVI; left atrial volume index, LVDd; left ventricular end-diastolic diameter, LVDs; left ventricular end-systolic diameter, LVEDV; left ventricular end diastolic volume, LVESV; left ventricular end systolic volume, LVEF; left ventricular ejection fraction, LVGLS; left ventricular global longitudinal strain, TRV; tricuspid regurgitation velocity.

s, $p < 0.05$). By contrast, there were no significant differences in LVEF, LVGLS and E/e' ratio between the follow-up period and the pre-AVR period.

3.2. Clinical characteristics of LV dysfunction group versus preserved LV function group after AVR

Table 2 shows the clinical characteristics of the LV dysfunction group and preserved LV function group in the follow-up period. There were no significant differences in baseline clinical characteristics, surgical procedures, and medications at discharge between the two groups. Regarding pre-AVR laboratory findings, CRP and neutrophils were significantly higher in the LV dysfunction group than in the preserved LV function group (CRP: 1.04 [0.14–4.25] vs. 0.07 [0.02–0.19], $p < 0.01$; neutrophils: 4606 [3450–8320] vs. 3215 [2594–4132], $p < 0.05$). In the echocardiographic findings from the pre-AVR period, LVDs and LVDs index were significantly higher, and LVEF and LVGLS were significantly lower, in the LV dysfunction group than in the preserved LV function group (LVDs: 49.6 ± 9.4 mm vs. 40.4 ± 7.7 mm, $p < 0.01$; LVDs index: 31.0 ± 4.4 mm/m2 vs. 25.9 ± 5.1 mm/m2, $p < 0.05$; LVEF: 45.7 ± 9.3 % vs. 57.7 ± 8.9 %, $p < 0.01$; LVGLS: 11.6 ± 3.2 vs. 15.2 ± 3.6, $p < 0.05$). EOA and mean transvalvular gradient after AVR were not significantly different between the 2 groups.

3.3. Significant factors associated with LV dysfunction in the follow-up period

Univariate logistic regression analysis revealed that natural logarithm (ln) CRP, LVDs, LVDs index, LVEF, and LVGLS in the pre-AVR period were significantly associated with LV dysfunction in the follow-up period (ln CRP: odds ratio (OR) 2.70, 95 % confidence interval (CI) 1.38–5.30, $p < 0.01$; LVDs: OR 1.15, 95 % CI 1.03–1.28, $p < 0.05$; LVDs index: OR 1.20, 95 % CI 1.03–1.40, $p < 0.05$; LVEF: OR 0.88, 95 % CI 0.80–0.97, $p < 0.01$; LVGLS: OR 0.75, 95 % CI 0.59–0.96, $p < 0.05$). Considering the internal correlation of LVDs, LVDs index, LVEF and LVGLS, we excluded LVDs, LVDs index and LVGLS from the multivariable logistic regression analysis. Multivariable logistic regression analysis showed that both ln CRP and LVEF in the pre-AVR period were significantly associated with LV dysfunction in the follow-up period (ln CRP: OR 4.15, 95 % CI 1.44–11.98, $p < 0.01$; LVEF: OR 0.79, 95 % CI 0.65–0.97, $p < 0.05$) (Table 3).

3.4. ROC analysis to predict LV dysfunction in the follow-up period

ROC analysis was performed to illustrate the diagnostic ability and determine the optimal cutoff value of CRP and LVEF during the pre-AVR

Table 2
Clinical characteristics between left ventricular dysfunction group and preserved left ventricular function group after aortic valve replacement.

	Left ventricular dysfunction group (n = 8)	Preserved left ventricular function group (n = 36)	p-value
Baseline clinical characteristics			
Age at surgery, years	70.0 ± 10.3	67.2 ± 13.1	0.57
Male sex, n (%)	6 (75)	22 (61)	0.46
Body mass index, kg/m^2	22.0 ± 2.8	22.5 ± 3.8	0.75
Past medical history			
Hypertension, n (%)	5 (63)	28 (78)	0.37
Diabetes mellitus, n (%)	1 (13)	1 (3)	0.23
Dyslipidemia, n (%)	3 (38)	13 (36)	0.94
Bicuspid valve, n (%)	3 (38)	6 (17)	0.19
Chronic atrial fibrillation, n (%)	0 (0)	1 (3)	0.63
Collagen diseases, n (%)	0 (0)	1 (3)	0.63
Ischemic heart diseases, n (%)	0 (0)	2 (6)	0.50
NYHA class ≥2, n (%)	4 (50)	18 (50)	1.00
Laboratory findings in the pre AVR period			
BNP	92.1 (26.0–146.2)	79.3 (43.9–153.7)	0.90
CRP	1.04 (0.14–4.25)	0.07 (0.02–0.19)	<0.01
eGFR, mL/min/1.73m^2	63.0 ± 26.3	64.5 ± 17.5	0.84
Hb level, g/dL	14.0 ± 2.6	12.9 ± 1.8	0.16
WBC, /uL	6700 (5025–10,125)	5550 (4550–6800)	0.12
Neutrophils, /uL	4606 (3450–8320)	3215 (2594–4132)	<0.05
Lymphocytes, /uL	1221 (844–1748)	1356 (1056–2036)	0.42
Monocytes, /uL	402 (286–530)	325 (275–378)	0.18
Eosinophils, /uL	180 (71–255)	118 (57–285)	0.74
Basophils, /uL	31 (12–46)	31 (20–49)	0.77
Echocardiographic findings in the pre AVR period			
LAVI, ml/m^2	41.1 ± 12.8	45.5 ± 12.9	0.39
IVSTd, mm	11.3 ± 1.2	11.3 ± 1.6	1.00
LVPWTd, mm	10.6 ± 1.6	11.3 ± 1.3	0.18
LVDd, mm	59.7 ± 6.9	57.1 ± 7.6	0.39
LVDs, mm	49.6 ± 9.4	40.4 ± 7.7	<0.01
LVDs index, mm/m^2	31.0 ± 4.4	25.9 ± 5.1	<0.05
LVEF, %	45.7 ± 9.3	57.7 ± 8.9	<0.01
LVGLS, %	11.6 ± 3.2	15.2 ± 3.6	<0.05
E/e' ratio	14.1 ± 10.4	12.3 ± 4.7	0.45
Severe AR, n (%)	4 (50)	27 (75)	0.16
Moderate MR, n (%)	0 (0)	1 (3)	0.63
Moderate TR, n (%)	0 (0)	3 (8)	0.40
Surgical procedure			
AVR only, n (%)	4 (50)	23 (64)	0.47
Biological valve, n (%)	4 (50)	21 (58)	0.67
Medication at discharge			
ACEI or ARB, n (%)	2 (25)	17 (47)	0.25
MRA, n (%)	0 (0)	5 (14)	0.26
β-blocker, n (%)	8 (100)	34 (94)	0.50
Ca blocker, n (%)	2 (25)	12 (33)	0.65
Echocardiographic findings in the follow-up period			
EOA, cm^2	1.60 ± 0.64	1.52 ± 0.37	0.67
Mean transvalvular gradient, mmHg	11.7 ± 5.5	11.0 ± 4.3	0.73

Abbreviations: AVR, aortic valve replacement; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin level; WBC, white blood cell; LAVI, left atrial volume index; IVSTd, interventricular septal thickness in diastole;

LVPWTd, left ventricular posterior wall thickness in diastole; LVDd; left ventricular end-diastolic diameter, LVDs; left ventricular end-systolic diameter, LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; EOA, effective orifice area.
The *p* values were obtained by student's-*t*-test, Mann-Whitney *U* test or chi-squared test.

period for predicting LV dysfunction in the follow-up period. As shown in Fig. 3a, the area under the curve (AUC) of CRP for LV dysfunction was 0.84. We also found that the best cutoff value of CRP was 0.13 mg/dL (sensitivity, 88 %; specificity, 69 %). Similarly, the AUC of LVEF for LV dysfunction was 0.83, and the best cutoff value of LVEF was 50 % (sensitivity, 83 %; specificity, 75 %) (Fig. 3b). The AUC of LVEF plus CRP for predicting LV dysfunction improved up to 0.94 (Fig. 3c).

3.5. Decision curve analysis

Fig. 4 demonstrated the decision curves for LVEF and LVEF plus CRP to predict LV dysfunction in the follow-up period. Although LVEF was useful to predict LV dysfunction between threshold probabilities of 0–30 %, LVEF plus CRP was more useful than only LVEF to predict LV dysfunction for most of the risk thresholds.

3.6. Predictive model for LV dysfunction in the follow-up period

We divided enrolled patients into four groups according to the cutoff value of CRP (0.13 mg/dL) and LVEF (50 %) in the pre-AVR period: low CRP (<0.13 mg/dL) and high LVEF (≥50 %) group ($n = 19$), low CRP (<0.13 mg/dL) and low LVEF (<50 %) group ($n = 7$), high CRP (≥0.13 mg/dL) and high LVEF (≥50 %) group ($n = 13$), and high CRP (≥0.13 mg/dL) and low LVEF (<50 %) group ($n = 5$). In the low CRP and high LVEF group, no patients had LV dysfunction in the follow-up period. By contrast, all patients in the high CRP and low LVEF group had LV dysfunction during the follow-up period (Figs. 4 and 5).

4. Discussion

A novel and main finding in the present study was that the combination of CRP and LVEF values was of significant use in predicting improved LV function after AVR.

In patients with AR, AVR was reported to have a useful effect on long-term survival [15] and LV reverse remodeling [16,17]. However, LV dysfunction in the pre-AVR period was associated with poor outcome after AVR [4,7]. In the present study, decreased LVEF (<50 %) in the pre-AVR period was significantly associated with LV dysfunction after AVR, indicating the importance of pre-AVR LV function. In addition, our study revealed that increased CRP levels were useful to predict LV dysfunction after AVR even after adjusting for LVEF.

CRP is a nonspecific, commonly used marker for inflammatory response. Inflammatory cells release cytokines, which stimulate hepatocytes to release CRP [18], which is associated with various types of cardiovascular disease. Moreover, inflammation plays an important role in all stages of the atherosclerotic process [19]. Therefore, atherosclerosis is usually considered a chronic inflammatory disease [20]. In valvular heart disease, AS has also been identified as an inflammatory-based condition [21], sharing common pathophysiology with atherosclerosis such as calcification, deposition of lipoproteins, and chronic inflammation. Persistently high levels of CRP have been associated with disease progression and increased cardiovascular mortality in patients with AS [22]. However, there have been only a few reports about the association between AR and inflammatory cytokines. Although we previously reported that increased CRP level was significantly associated with LV dysfunction in AR patients, all enrolled patients in that study had collagen diseases [9]. Accordingly in that study, we concluded

Table 3
Logistic regression analysis for left ventricular dysfunction in the follow-up period.

	Univariate analysis		Multivariable analysis	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Age per 1 year	1.02 (0.96–1.09)	0.57		
Male sex/ yes	1.91 (0.34–10.82)	0.47		
Body mass index per 1 kg/m^2	0.96 (0.77–1.21)	0.74		
Hypertension/ yes	0.48 (0.09–2.44)	0.37		
Diabetes mellitus/ yes	5.00 (0.28–89.80)	0.28		
Dyslipidemia/ yes	1.06 (0.22–5.18)	0.94		
Bicuspid valve/ yes	3.00 (0.56–16.07)	0.20		
NYHA class ≥2/yes	1.00 (1.00–1.00)	1.00		
Ln BNP per 1	0.96 (0.49–1.88)	0.90		
Ln CRP per 1	2.70 (1.38–5.30)	<0.01	4.15 (1.44–11.98)	<0.01
eGFR per 1 mL/min/ 1.73m^2	1.00 (0.96–1.04)	0.84		
Hb level per 1 mg/dL	1.37 (0.88–2.14)	0.16		
LAVI per 1 mL/m^2	0.97 (0.91–1.04)	0.38		
IVSTd per 1 mm	1.00 (0.60–1.66)	1.00		
LVPWTd per 1 mm	0.66 (0.37–1.21)	0.18		
LVDd per 1 mm	1.05 (0.94–1.18)	0.38		
LVDs per 1 mm	1.15 (1.03–1.28)	<0.05	*Not selected*	
LVDs index per 1 mm/m^2	1.20 (1.03–1.40)	<0.05	*Not selected*	
LVEF per 1 %	0.88 (0.80–0.97)	<0.01	0.79 (0.65–0.97)	<0.05
LVGLS per 1 %	0.75 (0.59–0.96)	<0.05	*Not selected*	
E/e' ratio per 1	1.04 (0.93–1.17)	0.45		
Severe AR	0.33 (0.07–1.62)	0.16		
AVR only/yes	0.57 (0.12–2.65)	0.47		
Biological valve/yes	0.72 (0.15–3.32)	0.67		
ACEI/ARB/yes	0.37 (0.07–2.10)	0.26		
MRA/yes	*Not selected*			
β-blocker/yes	*Not selected*			
EOA/1cm^2	1.58 (0.21–11.97)	0.66		
Mean transvalvular gradient/ 1 mmHg	1.03 (0.87–1.22)	0.72		

Laboratory findings and echocardiographic findings other than EOA and mean transvalvular gradient were obtained in the pre AVR period.
EOA and mean transvalvular gradient were obtained in the follow-up period.
Abbreviations: AVR, aortic valve replacement; NYHA, New York Heart Association; ln, natural logarithm; BNP, B-type natriuretic peptide; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LAVI, left atrial volume index; IVSTd, interventricular septal thickness in diastole; LVPWTd, left ventricular posterior wall thickness in diastole; LVDd; left ventricular end-diastolic diameter, LVDs; left ventricular end-systolic diameter, LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; EOA, effective orifice area.
P value was obtained by the logistic regression analyses model.

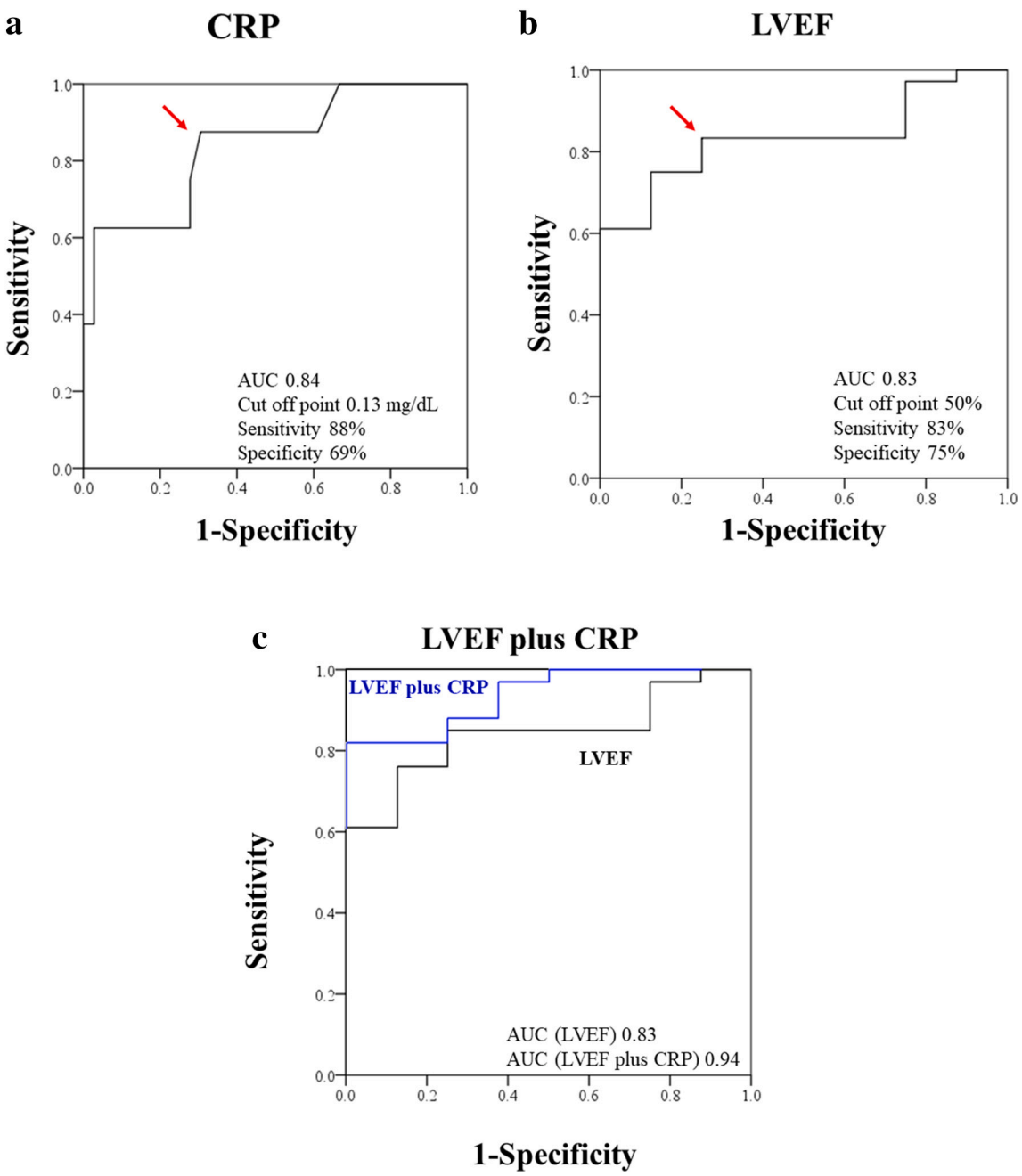

Fig. 3. Receiver-operator characteristic curve analysis of (a) CRP, (b) LVEF and (c) LVEF plus CRP for LV dysfunction in the follow-up period. Red arrow indicates cutoff point. CRP, C-reactive protein; AUC, area under the curve; LVEF, left ventricular ejection fraction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

that the association between high levels of CRP and LV dysfunction exists only in AR patients with collagen diseases. By contrast, in our present study only one AR patient had collagen disease and her LV function was preserved after AVR, indicating that collagen diseases might not be important regarding the association between CRP and LV dysfunction after AVR. Several studies showed that CRP is associated with an increased risk of cardiovascular events [23,24]. CRP is thought to reflect an important inflammatory component in the pathogenesis of ischemic heart disease [25]. To exclude the effect of ischemic heart disease on our present cohort, we excluded patients who underwent AVR and CABG simultaneously. Thus, only two patients had a history of ischemic heart disease, and these two patients were in the preserved LV function group after AVR. Therefore, we concluded that ischemic heart disease might not be irrelevant to the association between CRP and LV dysfunction in our present study.

Several studies have identified the importance of inflammation in the development and progression of heart failure [26]. Inflammation and heart failure are strongly interconnected and mutually reinforce each other [27]. Particularly in heart failure preserved ejection fraction (HFpEF), comorbidity-driven systemic microvascular inflammation is postulated to play a key role in the pathogenesis of myocardial structural and functional changes [28]. Because the average LVEF was 55 %, many patients in our present study were also considered to have HFpEF. Therefore, microvascular inflammation might exist among our patients. Several studies have shown the relationship between CRP and clinical outcome in HFpEF patients. CRP was associated with several proinflammatory cytokines and markers of heart failure severity and was predictive of all-cause and cardiovascular mortality [29]. Therefore,

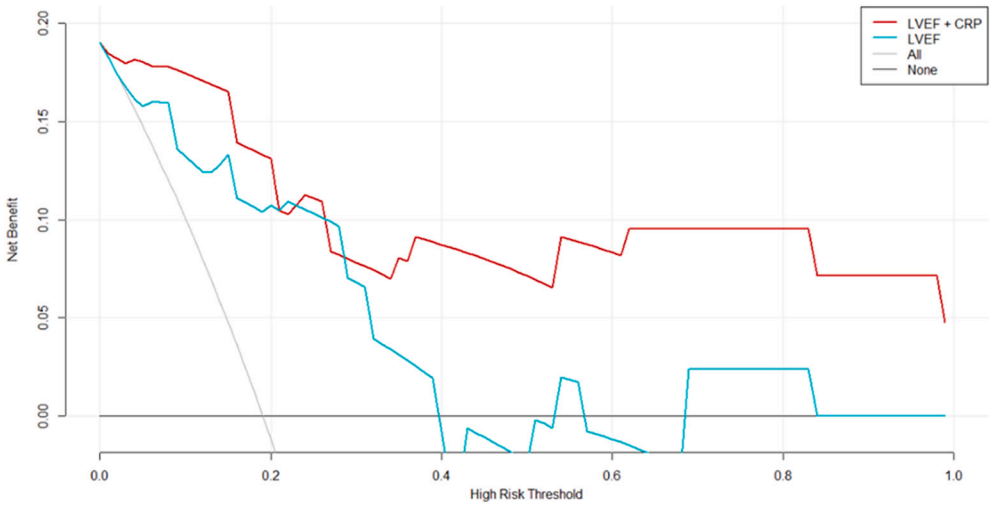

Fig. 4. Decision curves for LVEF and LVEF plus CRP to predict LV dysfunction in the follow-up period. The black line is the net benefit of treating no patients. The grey line is the net benefit of treating all patients. The blue line is the net benefit of treating patients according to LVEF. The red line is the net benefit of treating patients according to LVEF plus CRP.
LVEF, left ventricular ejection fraction; CRP, C-reactive protein; LV, left ventricle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

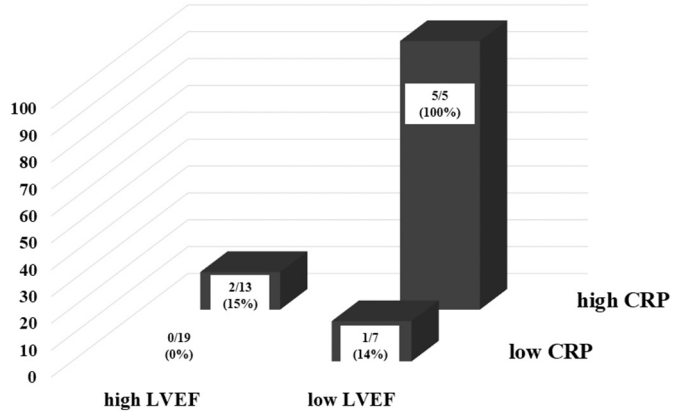

Fig. 5. Predictive model for LV dysfunction in the follow-up period. We divided the study patients into four groups according to CRP level and LVEF level: low CRP and high LVEF group ($n = 19$), low CRP and low LVEF group ($n = 7$), high CRP and low LVEF group ($n = 13$), and high CRP and low LVEF group ($n = 5$). LV, left ventricle; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.

cardiac structural change caused by AR was similar to HFpEF, which might be the reason why increased CRP was significantly associated with LV dysfunction after AVR. Even in AS patients, elevated inflammatory markers before transcatheter aortic valve implantation were associated with cardiac dysfunction in the follow-up period [30], indicated that inflammation in the pre-AVR period was important for cardiac dysfunction after AVR in patients both with AR and AS.

ACEIs, ARBs, MRAs, and β-blockers have been widely used for cardiac protection in patients with heart failure [31–34]. In the present study, however, ACEIs or ARBs and MRAs were not fully prescribed to patients in the LV dysfunction group. Our results indicated that the combination of low LVEF and high CRP was useful in predicting cardiac dysfunction after AVR. Thus, we are minded to prescribe adequate medical therapy that includes ACEIs, ARBs, and MRAs to patients with low LVEF and high CRP levels during the pre-AVR period.

4.1. Study limitations

The present study has several limitations. First, we enrolled a relatively small number of patients and carried out the study at a single center. Second, we did not evaluate AR volume for all enrolled patients. The proximal isovelocity surface area method and volumetric method are used for quantitative analysis of the severity of AR. Many patients could not undergo these quantitative analyses because the proximal isovelocity surface area method is not valid for multiple or eccentric jets and the volumetric method is not valid for patients with aortic valve or mitral annulus calcification because it is difficult to measure LV outflow tract diameter or mitral annulus diameter. Therefore, we evaluated the severity of AR comprehensively by using quantitative and qualitative methods. Third, 75 % of the preserved LV function group in the follow-up period had severe AR prior to surgery. In contrast, only 50 % of those had severe AR in the reduced LV function group. This result suggested that concealed cardiomyopathy might be more in the reduced LV function group than in the preserved LV function group. Although cardiac biopsy or cardiac magnetic resonance imaging is necessary to exclude cardiomyopathy, these procedures were not available to many patients in our present study. Therefore, we could not compare the rate of concealed cardiomyopathy between reduced LV function group and preserved LV function group. This point was an important limitation of our present study. Forth, the comparison between AVR population and non-AVR population might be useful to emphasis the usefulness of CRP level for LV dysfunction after AVR. However, in our present study, we focused on the time-dependent change of cardiac function between pre and post AVR periods in AR patients. Therefore, we did not include non-AVR population in our present study to avoid confusion. Future prospective multicenter study may be need to evaluate the difference of CRP utility between AVR population and non-AVR population. Despite these limitations, our study is unique in showing the importance of CRP levels in predicting LV dysfunction after AVR in AR patients.

5. Conclusion

A high CRP level was significantly associated with LV dysfunction after AVR, even after adjusting for LVEF. A combination of CRP and LVEF values might be useful for the prediction of LV functional improvement after AVR.

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Ethics approval

This study was approved by the institutional review board and ethics committee of Kumamoto University (Reference number: 1588).

CRediT authorship contribution statement

Individual contribution to this article

Hiroki Usuku: Study conception and design, analysis of data, drafting of manuscript

Fumi Oike: Drafting of manuscript

Eiichiro Yamamoto: Drafting of manuscript

Naoko Kai: Analysis of data

Koichi Egashira: Drafting of manuscript

Takashi Komorita: Drafting of manuscript

Kyoko Hirakawa: Drafting of manuscript

Shozo Kaneko: Drafting of manuscript

Noriaki Tabata: Drafting of manuscript

Masanobu Ishii: Analysis of data

Kenshi Yamanaga: Drafting of manuscript

Koichiro Fujisue: Drafting of manuscript

Shinsuke Hanatani: Drafting of manuscript

Tadashi Hoshiyama: Drafting of manuscript

Hisanori Kanazawa: Drafting of manuscript

Daisuke Sueta: Drafting of manuscript

Yuichiro Arima: Drafting of manuscript

Seiji Takashio: Drafting of manuscript

Hiroaki Kawano: Drafting of manuscript

Kenichi Matsushita: Drafting of manuscript

Toshihiro Fukui: Drafting of manuscript

Hirotaka Matusi: Drafting of manuscript

Kenichi Tsujita: Drafting of manuscript

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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References

[1] T. Wisenbaugh, J.F. Spann, B.A. Carabello, Differences in myocardial performance and load between patients with similar amounts of chronic aortic versus chronic mitral regurgitation, J. Am. Coll. Cardiol. 3 (1984) 916–923, https://doi.org/10.1016/s0735-1097(84)80349-6.

[2] B.A. Carabello, Aortic regurgitation. A lesion with similarities to both aortic stenosis and mitral regurgitation, Circulation 82 (1990) 1051–1053, https://doi.org/10.1161/01.cir.82.3.1051.

[3] K. Disha, A. Espinoza, M. Rouman, M.A. Secknus, T. Kuntze, E. Girdauskas, Long-term recovery of reduced left ventricular ejection fraction after aortic valve replacement in patients with bicuspid aortic valve disease, Thorac. Cardiovasc. Surg. 64 (2016) 418–426, https://doi.org/10.1055/s-0035-1557114.

[4] M.L. Brown, H.V. Schaff, R.M. Suri, Z. Li, T.M. Sundt, J.A. Dearani, et al., Indexed left ventricular dimensions best predict survival after aortic valve replacement in patients with aortic valve regurgitation, Ann. Thorac. Surg. 87 (2009) 1170–1175, https://doi.org/10.1016/j.athoracsur.2008.12.086, discussion 1175–1176.

[5] R.A. Nishimura, C.M. Otto, R.O. Bonow, B.A. Carabello, J.P. Erwin III, R.A. Guyton, et al., 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, Circulation 129 (2014) e521–e643, https://doi.org/10.1161/cir.0000000000000031.

[6] H. Baumgartner, V. Falk, J.J. Bax, M. De Bonis, C. Hamm, P.J. Holm, et al., 2017 ESC/EACTS guidelines for the management of valvular heart disease, Eur. Heart J. 38 (2017) 2739–2791, https://doi.org/10.1093/eurheartj/ehx391.

[7] J. Petersen, N. Neumann, S. Naito, T. Sequeira Gross, R. Massel, H. Reichenspurner, et al., Persistence of reduced left ventricular function after aortic valve surgery for aortic valve regurgitation: bicuspid versus tricuspid, Thorac. Cardiovasc. Surg. 69 (2021) 389–395, https://doi.org/10.1055/s-0039-1692664.

[8] C. Izumi, T. Kitai, T. Kume, T. Onishi, S. Yuda, K. Hirata, et al., Effect of left ventricular reverse remodeling on long-term outcomes after aortic valve replacement, Am. J. Cardiol. 124 (2019) 105–112, https://doi.org/10.1016/j.amjcard.2019.04.010.

[9] H. Usuku, E. Yamamoto, M. Noguchi, T. Komorita, M. Takae, F. Oike, et al., Elevated C-reactive protein is significantly associated with left ventricular dysfunction in patients with aortic regurgitation and concomitant collagen disease, Int. J. Cardiol. 328 (2021) 152–157, https://doi.org/10.1016/j.ijcard.2020.12.053.

[10] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (2015) 1–39.e14, https://doi.org/10.1016/j.echo.2014.10.003.

[11] S.F. Nagueh, O.A. Smiseth, C.P. Appleton, B.F. Byrd III, H. Dokainish, T. Edvardsen, et al., Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 29 (2016) 277–314, https://doi.org/10.1016/j.echo.2016.01.011.

[12] W.A. Zoghbi, D. Adams, R.O. Bonow, M. Enriquez-Sarano, E. Foster, P.A. Grayburn, et al., Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance, J. Am. Soc. Echocardiogr. 30 (2017) 303–371, https://doi.org/10.1016/j.echo.2017.01.007.

[13] W.A. Zoghbi, J.B. Chambers, J.G. Dumesnil, E. Foster, J.S. Gottdiener, P. A. Grayburn, et al., Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography, J. Am. Soc. Echocardiogr. 22 (2009) 975–1014, https://doi.org/10.1016/j.echo.2009.07.013, quiz 1082-1014.

[14] A.J. Vickers, E.B. Elkin, Decision curve analysis: a novel method for evaluating prediction models, Med. Decis. Mak. 26 (2006) 565–574, https://doi.org/10.1177/0272989x06295361.

[15] A.R. Kamath, P. Varadarajan, R. Turk, U. Sampat, R. Patel, S. Khandhar, et al., Survival in patients with severe aortic regurgitation and severe left ventricular dysfunction is improved by aortic valve replacement: results from a cohort of 166 patients with an ejection fraction < or =35%, Circulation 120 (2009) S134–S138, https://doi.org/10.1161/circulationaha.108.839787.

[16] A. Haverich, T.C. Wahlers, M.A. Borger, M. Shrestha, A.A. Kocher, T. Walther, et al., Three-year hemodynamic performance, left ventricular mass regression, and prosthetic-patient mismatch after rapid deployment aortic valve replacement in 287 patients, J. Thorac. Cardiovasc. Surg. 148 (2014) 2854–2860, https://doi.org/10.1016/j.jtcvs.2014.07.049.

[17] M. Amano, C. Izumi, S. Imamura, N. Onishi, Y. Tamaki, S. Enomoto, et al., Late recurrence of left ventricular dysfunction after aortic valve replacement for severe chronic aortic regurgitation, Int. J. Cardiol. 224 (2016) 240–244, https://doi.org/10.1016/j.ijcard.2016.09.032.

[18] M.B. Pepys, C-reactive protein fifty years on, Lancet 1 (1981) 653–657, https://doi.org/10.1016/s0140-6736(81)91565-8.

[19] P. Libby, P.M. Ridker, G.K. Hansson, Progress and challenges in translating the biology of atherosclerosis, Nature 473 (2011) 317–325, https://doi.org/10.1038/nature10146.

[20] R. Ross, Atherosclerosis–an inflammatory disease, N. Engl. J. Med. 340 (1999) 115–126, https://doi.org/10.1056/nejm199901143400207.

[21] A. Galante, A. Pietroiusti, M. Vellini, P. Piccolo, G. Possati, M. De Bonis, et al., C-reactive protein is increased in patients with degenerative aortic valvular stenosis, J. Am. Coll. Cardiol. 38 (2001) 1078–1082, https://doi.org/10.1016/s0735-1097(01)01484-x.

[22] K. Imai, H. Okura, T. Kume, R. Yamada, Y. Miyamoto, T. Kawamoto, et al., C-reactive protein predicts severity, progression, and prognosis of asymptomatic aortic valve stenosis, Am. Heart J. 156 (2008) 713–718, https://doi.org/10.1016/j.ahj.2008.04.011.

[23] P.M. Ridker, M. Cushman, M.J. Stampfer, R.P. Tracy, C.H. Hennekens, Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men, N. Engl. J. Med. 336 (1997) 973–979, https://doi.org/10.1056/nejm199704033361401.

[24] P.M. Ridker, C.H. Hennekens, J.E. Buring, N. Rifai, C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women, N. Engl. J. Med. 342 (2000) 836–843, https://doi.org/10.1056/nejm200003233421202.

[25] G. Liuzzo, L.M. Biasucci, J.R. Gallimore, R.L. Grillo, A.G. Rebuzzi, M.B. Pepys, et al., The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina, N. Engl. J. Med. 331 (1994) 417–424, https://doi.org/10.1056/nejm199408183310701.

[26] D.L. Mann, Inflammatory mediators and the failing heart: past, present, and the foreseeable future, Circ. Res. 91 (2002) 988–998, https://doi.org/10.1161/01.res.0000043825.01705.1b.

[27] S. Van Linthout, C. Tschöpe, Inflammation - cause or consequence of heart failure or both? Curr. Heart Fail. Rep. 14 (2017) 251–265, https://doi.org/10.1007/s11897-017-0337-9.

[28] W.J. Paulus, C. Tschöpe, A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation, J. Am. Coll. Cardiol. 62 (2013) 263–271, https://doi.org/10.1016/j.jacc.2013.02.092.

[29] L. Koller, M. Kleber, G. Goliasch, P. Sulzgruber, H. Scharnagl, G. Silbernagel, et al., C-reactive protein predicts mortality in patients referred for coronary angiography and symptoms of heart failure with preserved ejection fraction, Eur. J. Heart Fail. 16 (2014) 758–766, https://doi.org/10.1002/ejhf.104.

[30] J. Hoffmann, S. Mas-Peiro, A. Berkowitsch, F. Boeckling, T. Rasper, K. Pieszko, et al., Inflammatory signatures are associated with increased mortality after transfemoral transcatheter aortic valve implantation, ESC Heart Fail. 7 (2020) 2597–2610, https://doi.org/10.1002/ehf2.12837.

[31] Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), N. Engl. J. Med. 316 (1987) 1429–1435, https://doi.org/10.1056/nejm198706043162301.

[32] C.B. Granger, J.J. McMurray, S. Yusuf, P. Held, E.L. Michelson, B. Olofsson, et al., Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial, Lancet 362 (2003) 772–776, https://doi.org/10.1016/s0140-6736(03)14284-5.

[33] B. Pitt, W. Remme, F. Zannad, J. Neaton, F. Martinez, B. Roniker, et al., Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction, N. Engl. J. Med. 348 (2003) 1309–1321, https://doi.org/10.1056/NEJMoa030207.

[34] M. Packer, A.J. Coats, M.B. Fowler, H.A. Katus, H. Krum, P. Mohacsi, et al., Effect of carvedilol on survival in severe chronic heart failure, N. Engl. J. Med. 344 (2001) 1651–1658, https://doi.org/10.1056/nejm200105313442201.