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Usefulness of platelet count to predict concomitant valvular heart disease in patients with systemic lupus erythematosus

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ABSTRACT

Background: Although the prevalence rate of valvular heart disease (VHD) is high in patients with systemic lupus erythematosus (SLE), the predictive factors of concomitant VHD have not been fully evaluated.
Methods and results: Among 288 patients with SLE who underwent transthoracic echocardiography at Kumamoto University Hospital from 2016 to 2021, 241 patients with sufficient echocardiographic data were retrospectively analysed. Among them, 22 (9 %) had VHD (10 had mitral regurgitation, 3 had aortic regurgitation, 6 had tricuspid regurgitation, 1 had mitral regurgitation and tricuspid regurgitation, and 2 had a prosthetic cardiac valve). After excluding the two patients with a prosthetic cardiac valve, we divided the remaining patients into two groups: the VHD group and non-VHD group. Multivariate logistic regression analysis revealed that age and the platelet count were significantly and independently associated with having VHD (age: odds ratio, 1.06; 95 % confidence interval, 1.02–1.10; $p < 0.01$) (platelet count: odds ratio, 0.99; 95 % confidence interval, 0.98–1.00; $p < 0.05$). After excluding 95 patients aged < 40 years, receiver operating characteristic analysis revealed that the area under the curve of the platelet count for prediction of VHD was 0.73 with an optimal cut-off value of $166.5 \times 10^3/\mu L$ (sensitivity: 76.6 %, specificity: 60.0 %). Among patients with a low platelet count ($<166.5 \times 10^3/\mu L$), the rate of having VHD was 29 % (12/41 patients). However, among those with a high platelet count ($\geq 166.5 \times 10^3/\mu L$), this rate was only 8 % (8/103 patients).
Conclusion: The platelet count is useful to predict concomitant VHD in middle-aged and older patients with SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease of variable severity and progression. SLE exhibits marked female predominance, with almost 10 women affected for every man with the disease. The incidence ranges from 0.3 to 31.5 cases per 100,000 individuals per year and has increased during the last 40 years, probably because of recognition of milder cases [1]. SLE is an independent risk factor for cardiovascular disease, attributed both to traditional and disease-related risk factors [2]. In particular, the prevalence rate of valvular heart disease (VHD) is higher in patients with SLE than in the general population [3,4]. Hypertension, dyslipidaemia, high disease activity, and high glucocorticoid doses are associated with a high risk of cardiovascular disease in patients with SLE [5–8]. In addition, Libman–Sacks endocarditis, characterised by non-bacterial verrucous vegetations with SLE, is a major cause of VHD [9]. However, the clinical course and survival of SLE have dramatically improved in recent years [10–13]. Therefore, the prevalence and predictors of VHD in patients

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with SLE is considered to be changing.

The present study was performed to evaluate the predictive factors of concomitant VHD in patients with SLE.

2. Methods

2.1. Study population

This study was conducted at Kumamoto University Hospital in Japan. Transthoracic echocardiography was performed in 288 patients with SLE from 2016 to 2021. Of these patients, 47 were excluded because they had insufficient echocardiographic data. The remaining 241 patients with SLE were enrolled in the present study. Baseline clinical characteristics, laboratory findings, and echocardiographic data were obtained while the patients were clinically stable. Implantation of a prosthetic cardiac valve into the circulation alters the haemodynamics and quickly initiates plasmatic and cellular response, lead to thromboembolic complications [14]. Then we excluded patients with a prosthetic cardiac valve and divided the remained patients into two groups according to the presence or absence of VHD.

This study conformed to the principles outlined in the Declaration of Helsinki and was approved by the institutional review board and ethics committee of Kumamoto University (No. 2254). The requirement to obtain informed consent was waived because of the low-risk nature of this retrospective study regarding patient identification and the inability to obtain consent directly from all patients. Instead, we extensively announced the 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. Definitions of clinical characteristics

SLE was diagnosed by a rheumatologist according to the revised American College of Rheumatology [15] or Systemic Lupus International Collaborating Clinics [16] classification criteria for SLE. The modified SLE disease activity index (SLEDAI), an important scoring system used to evaluate SLE activity, was evaluated by a rheumatologist according to a previous report [17]. Other connective tissue diseases, including rheumatoid arthritis, Sjögren's syndrome, scleroderma, dermatomyositis/polymyositis, and mixed connective tissue disease, were diagnosed by a rheumatologist according to the relevant guidelines [18–22]. Antiphospholipid syndrome (APS) was defined as a medium to high titre of an anticardiolipin antibody of the immunoglobulin (Ig) G and/or IgM isotype (>40 U/mL or >99th percentile) or a high titre of an anti-β2-glycoprotein I antibody of the IgG and/or IgM isotype (>99th percentile) [23]. Ischaemic heart disease (IHD), VHD, hypertrophic cardiomyopathy (HCM), and congenital heart disease were included as cardiac diseases. IHD was defined as diagnosis of myocardial infarction, angina pectoris, asymptomatic myocardial ischaemia, or vasospastic angina by a cardiologist. We defined VHD when the severity was moderate or severe in the present study in accordance with the American Society of Echocardiography guideline [24]. HCM was diagnosed by a cardiologist according to the Japanese Circulation Society/Japanese Heart Failure Society guideline [25]. Congenital heart diseases were diagnosed by a cardiologist on the basis of the transthoracic echocardiography findings.

2.3. Echocardiographic measurements

Echocardiography was performed at the discretion of the attending physician using a Vivid E95 or 7 (GE Vingmed, Horten, Norway), Aplio 500 (Canon Medical Systems Corp., Otawara, Tochigi, Japan), or Epiq 7G (Philips, Bothell, WA, USA), each of which was equipped with a 2.5-MHz phased-array transducer. For patients who underwent multiple imaging examinations, we selected the final echocardiographic data for analysis. Echocardiography was performed in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [26,27]. The left ventricular (LV) wall thickness was acquired in the parasternal long-axis view. The LV ejection fraction and left atrial volume index (LAVI) were calculated using a modified Simpson's method. Peak early diastolic velocity of LV inflow (E velocity) and peak early diastolic velocity on the average of septal and lateral corner of the mitral annulus (e′) were measured in the apical four-chamber view. To minimise bias, the echocardiography reviewers were blinded to the patients' clinical history and data.

2.4. Data collection

Laboratory examination and echocardiography were performed on the same day in the majority of enrolled patients (interquartile range, 0–1 day). Blood samples were collected early in the morning in fasted patients. The blood samples were then stored at −80°C before analysis of biochemical parameters. Anticardiolipin antibody was measured by an enzyme-linked immunosorbent assay, and anti-β2-glycoprotein I antibody was measured by an enzyme immunoassay [23]. Echocardiographic findings, the SLEDAI, and current medications were ascertained by reviewing the medical records.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation. Non-normally distributed variables are presented as median (interquartile range). Categorical variables are presented as frequency or percentage. The patients' clinical characteristics were compared between the VHD group and non-VHD group using Student's-t test, the Mann–Whitney U test, or the chi-squared test. Univariate and multivariate logistic regression analyses were performed to identify the independent parameters related to VHD and to assess the degree of association. Variables with a p-value of <0.05 in the univariate logistic regression analysis were incorporated into the multivariable logistic regression analysis. The area under the curve obtained by receiver operating characteristic analysis was calculated to assess the ability of the platelet count to predict VHD. Statistical analyses were performed with SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). A two-tailed p value of <0.05 denoted a statistically significant difference.

3. Results

3.1. Prevalence of cardiac disease in patients with SLE

Supplemental figure 1a shows the number of cardiac diseases among patients with SLE. Among the 241 enrolled patients, 45 patients had cardiac disease. Supplemental figure 1b shows the number of patients with each type of cardiac disease. Seventeen patients had VHD, 15 had IHD, 6 had HCM, 2 had congenital heart disease, 3 had both IHD and VHD, and 2 had both VHD and HCM. Among the 22 patients with VHD, 10 had mitral regurgitation, 3 had aortic regurgitation, 6 had tricuspid regurgitation, 1 had mitral regurgitation and tricuspid regurgitation, and 2 had a prosthetic cardiac valve. Among the 18 patients with IHD, 7 had myocardial infarction, 6 had angina pectoris or asymptomatic myocardial ischaemia, and 5 had vasospastic angina. Coronary angiography was performed in 14 of these 18 patients, coronary computed tomography was performed in 10, cardiac scintigraphy was performed in 14, and 1 patient was diagnosed with IHD by their medical history alone.

figure 1a shows the distribution of SLE by age. The number of patients with SLE was highest between the ages of 40 and 50 years. figure 1b shows the distribution of VHD by age. No patients aged <40 years had VHD. Thereafter, the rate of VHD increased according to age.

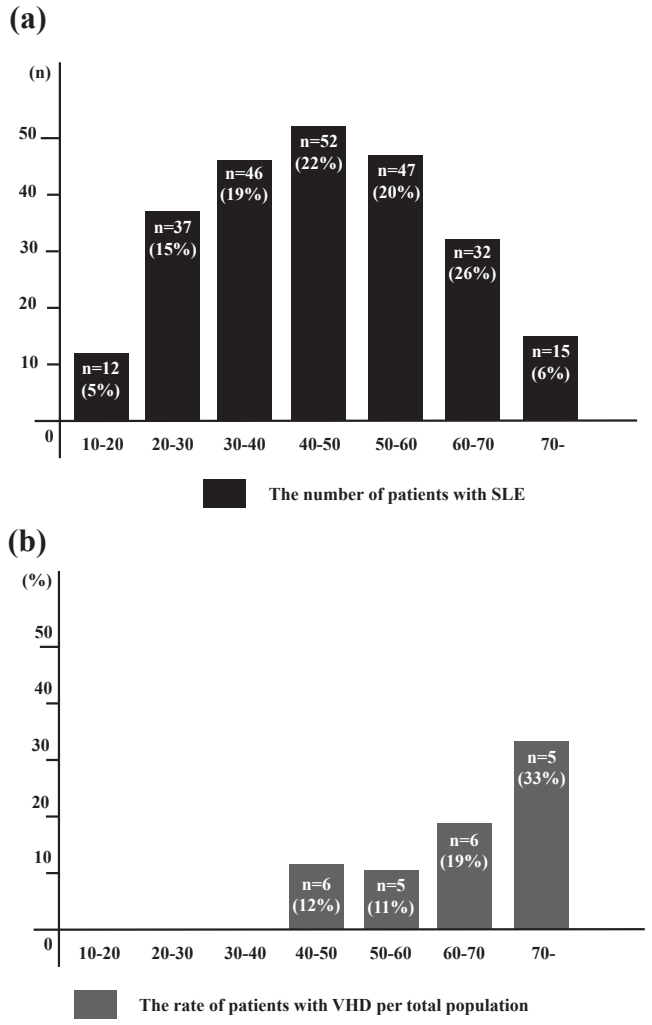

Fig. 1. Distributions of (a) patients with SLE by age and (b) those with VHD by age. SLE, systemic lupus erythematosus; VHD, valvular heart disease.

3.2. Comparison of clinical characteristics between VHD and non-VHD groups

After we excluded the two patients with a prosthetic cardiac valve, we divided the remaining patients into two groups: the VHD group and non-VHD group. Table 1 shows the clinical characteristics, laboratory findings, echocardiographic findings, cardiac treatments, and therapeutic agents for connective tissue diseases in the VHD and non-VHD groups. Patients in the VHD group were older and had longer duration of SLE disease, lower body mass index (BMI), and higher incidence of hypertension than those in non-VHD group (age: 59.5 ± 14.1 vs. 43.5 ± 15.8 years, $p < 0.01$; duration of SLE disease: 25.4 ± 13.6 vs. 12.9 ± 10.9 years, $p < 0.01$; BMI: 19.0 ± 2.4 vs. 22.4 ± 4.8 kg/m^2, $p < 0.01$; and hypertension: 70 % vs. 42 %, $p < 0.05$). However, there were no significant differences in concomitant connective tissue diseases or the SLEDAI between the two groups. Among the laboratory findings, the platelet count and estimated glomerular filtration rate (eGFR) were significantly lower, and total bilirubin and AST were significantly higher in the VHD than non-VHD group (platelet count: 162.8 ± 45.0 vs. 223.6 ± 73.1 × 10^3/μL, $p < 0.01$, eGFR: 56.0 ± 26.8 vs. 74.5 ± 19.3 mL/min/1.73 m^2, $p < 0.01$, total bilirubin: 0.70 [0.50–1.08] vs. 0.60 [0.40–0.70], $p<0.05$ and AST: 25.0 [20.0–34.0] vs. 20.0 [16.0–27.0], $p<0.01$). Among the echocardiographic findings, the LAVI was lower and the interventricular septal thickness in diastole (IVSTd), LV posterior wall thickness in diastole (LVPWTd), and tricuspid regurgitation pressure

Table 1
Clinical characteristics between VHD group and non-VHD group.

	Total patients (n=239)	VHD group (n=20)	Non-VHD group (n=219)	p-value
Baseline clinical characteristics				
Age, years	44.8±16.3	59.5±14.1	43.5±15.8	<0.01
Duration of SLE disease, years	13.9±11.7	25.4±13.6	12.9±10.9	<0.01
Male sex, n (%)	27 (11)	1 (5)	26 (12)	0.35
Systolic BP, mmHg	118.8 ±17.1	118.7±20.7	118.8±16.8	0.99
Diastolic BP, mmHg	73.6±15.9	76.8±18.3	73.3±15.7	0.36
Heart rate, bpm	73.1±12.5	70.7±17.7	73.3±12.0	0.38
Body mass index, kg/m^2	22.1±4.7	19.0±2.4	22.4±4.8	<0.01
Past medical history				
Hypertension, n (%)	107 (45)	14 (70)	93 (42)	<0.05
Diabetes mellitus, n (%)	28 (12)	1 (5)	27 (12)	0.33
Dyslipidemia, n (%)	70 (29)	7 (35)	63 (29)	0.56
Arial fibrillation, n (%)	4 (2)	0 (0)	4 (2)	0.54
Dialysis, n (%)	5 (2)	1 (5)	4 (2)	0.34
Rheumatoid arthritis, n (%)	14 (6)	1 (5)	13 (6)	0.87
Sjögren syndrome, n (%)	64 (27)	3 (15)	61 (28)	0.21
Scleroderma, n (%)	20 (8)	2 (10)	18 (8)	0.78
Dermatomyositis/ polymyositis, n (%)	8 (3)	0 (0)	8 (4)	0.39
MCTD, n (%)	9 (4)	1 (5)	8 (4)	0.76
SLEDAI	10.1±7.3 (n=211)	9.4±6.4 (n=17)	10.2±7.4 (n=194)	0.67
Laboratory findings				
White blood cell count/ uL	5700 [4200-9100]	5550 [3750-9100]	5700 [4200-7200]	0.67
Hemoglobin level, g/dL	12.3±1.7	11.9±1.8	12.3±1.7	0.29
Platelet count/uL	218.5 ±73.1	162.8 ±45.0x10^3	223.6 ±73.1x10^3	<0.01
eGFR, mL/min/1.73m^2	72.6±21.1	56.0±26.8	74.5±19.3	<0.01
Total bilirubin, mg/dL	0.60 [0.50-0.70]	0.70 [0.50-1.08]	0.60 [0.40-0.70]	<0.05
AST, U/L	20.0 [16.0-27.0]	25.0 [20.0-34.0]	20.0 [16.0-27.0]	<0.01
ALT, U/L	17.0 [12.0-24.0]	18.0 [15.3-23.0]	16.0 [11.0-24.0]	0.28
C reactive protein, mg/L	0.08[0.02-0.24]	0.14 [0.03-0.65]	0.08 [0.02-0.24]	0.21
CH 50, /mL	47.0[36.5-57.0]	56.5 [41.3-62.3]	47.0 [36.0-56.0]	0.06
C3, mg/dL	80.5[65.0-99.3]	87.4 [64.8-96.9]	80.3 [65.0-99.4]	0.97
C4, mg/dL	16.8[10.2-22.5]	16.5 [12.5-24.8]	16.8 [9.9-22.5]	0.55
Anti-double stranded DNA IgG antibody, IU/ml	2.5[1.1-8.0]	2.6 [1.1-4.9]	2.5 [1.1-8.1]	0.57
Antiphospholipid antibody syndrome, n (%)	49 (21)	3 (15)	46 (22)	0.46
Echocardiographic findings				
LAVI, ml/m^2	29.7±13.2	39.8±15.8	28.7±12.6	<0.01
IVSTd, mm	9.1±2.0	10.2±2.0	9.0±1.9	<0.05
LVPWTd, mm	9.0±1.5	9.8±1.8	8.9±1.5	<0.01
LVEF, %	63.9±5.0	64.5±6.2	63.9±4.9	0.6
E/e' ratio	8.19±4.89	9.93±4.30	8.03±4.91	0.12
TRPG, mmHg	21.2±7.5	29.7±16.9	20.4±5.4	<0.01
Cardiac treatment				
RAS inhibitor, n (%)	66 (28)	6 (30)	60 (27)	0.8
Beta blocker, n (%)	24 (10)	7 (35)	17 (8)	<0.01
MRA, n (%)	8 (3)	0 (0)	8 (4)	0.39

(*continued on next page*)

Table 1 (*continued*)

	Total patients (n=239)	VHD group (n=20)	Non-VHD group (n=219)	p-value
Therapeutic agent for collagen diseases				
Glucocorticoids, n (%)	209 (87)	18 (90)	191 (87)	0.72
Prednisolone equivalent amount, mg	7.45±7.69	6.75±4.03	7.61±7.94	0.63
Immunosuppressant, n (%)	111 (46)	5 (25)	106 (48)	<0.05
Mizoribine, n	16	3	13	<0.05
Tacrolimus hydrate, n	56	1	55	
Azathioprine, n	17	1	16	
Methotrexate, n	7	0	7	
Immunomodulator, n	90 (38)	5 (25)	85 (39)	0.22
Hydroxychloroquine Sulfate, n	87	5	82	
Iguratimod, n	3	0	3	
Bucillamine, n	1	0	1	
Salazosulfapyridine, n	1	0	1	

Abbreviations: VHD, valvular heart disease; BP, blood pressure; MCTD, mixed connective tissue disease; SLDAI, systemic lupus erythematous disease activity index; eGFR, estimated glomerular filtration rate; DNA, deoxyribo nucleic acid; LAVI, left atrial volume index; IVSTd, interventricular septal thickness in diastole; LVPWTd, left ventricular posterior wall thickness in diastole; LVEF, left ventricular ejection fraction; TRPG, tricuspid regurgitation pressure gradient; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist.
The p values were obtained by student's-t test, Mann-Whitney U test or chi-squared test.

gradient (TRPG) were higher in the VHD than non-VHD group (LAVI: 28.7 ± 12.6 vs. 39.8 ± 15.8 mL/m^2, $p < 0.01$; IVSTd: 10.2 ± 2.0 vs. 9.0 ± 1.9 mm, $p < 0.05$; LVPWTd: 9.8 ± 1.8 vs. 8.9 ± 1.5 mm, $p < 0.01$; and TRPG, 29.7 ± 16.9 vs. 20.4 ± 5.4 mmHg, $p < 0.01$). With respect to cardiac treatments, the rate of beta blocker therapy was significantly higher in the VHD than non-VHD group (35 % vs. 8 %, $p < 0.01$). With respect to therapeutic agents for connective tissue disease, there was no significant difference in the rate of glucocorticoid use or the prednisolone-equivalent dose between the two groups. However, the rate of immunosuppressant therapy was significantly lower in the VHD than non-VHD group (25 % vs. 48 %, $p < 0.05$).

3.3. Logistic regression analysis for having VHD

As shown in Table 2a, the univariate logistic regression analysis showed that 13 variables were significantly associated with having VHD: age, duration of SLE disease, BMI, hypertension, eGFR, total bilirubin, platelet count, LAVI, IVSTd, LVPWTd, TRPG, beta blocker therapy, and immunosuppressant therapy. Considering the internal correlation and the number of patients in our study, we created five models with which to perform a multivariate logistic regression analysis (Table 2b). The platelet count was significantly and independently associated with having VHD after adjusting for age, duration of SLE disease, BMI, and hypertension (Model 1); LAVI, IVSTd, and TRPG (Model 2); eGFR and total bilirubin (Model 3); beta blocker therapy (Model 4); and immunosuppressant therapy (Model 5).

3.4. Receiver operating characteristic analysis of platelet count for having VHD

We excluded 95 patients aged <40 years because they did not have VHD. The subsequent receiver operating characteristic analysis revealed that the area under the curve of the platelet count was 0.73 with an optimal cut-off value of 166.5 × 10^3/μL (sensitivity: 76.6 %, specificity: 60.0 %) for prediction of VHD (Fig. 2). Using this cut-off value, the rate of having VHD in patients with a platelet count of <166.5 × 10^3/μL was 29 % (12/41 patients), whereas that in patients with a platelet count of ≥166.5 × 10^3/μL was only 8 % (8/103 patients) (Supplemental figure 2). In enrolled total patients, platelet count < 166.5x10^3/uL was significantly and independently associated with having VHD after adjusting for age, duration of SLE disease, BMI and hypertension (odds ratio 8.11, 95% CI 2.38–27.64, p<0.01) (Model 1) and adjusting for LAVI, IVSTd and TRPG (odds ratio 4.11, 95 % CI 1.44–11.70, p<0.01) (Model 2) (Supplemental table 1) by multivariable logistic regression analysis.

Table 2a
Univariate Logistic Regression Analysis for having VHD

	Univariate analysis	
	HR (95% CI)	P-value
Age per 1 year	1.07 (1.03-1.10)	<0.01
Duration of SLE disease per 1 year	1.08 (1.04-1.12)	<0.01
Male sex/ yes	0.39 (0.05-3.04)	0.37
Systolic BP per 1mmHg	1.00 (0.97-1.03)	0.99
Diastolic BP per 1mmHg	1.01 (0.98-1.05)	0.36
Heart rate per 1bpm	0.99 (0.95-1.03)	0.55
Body mass index per 1kg/m^2	0.76 (0.65-0.91)	<0.01
Hypertension/ yes	3.14 (1.16-8.47)	<0.05
Diabetes mellitus/ yes	0.37 (0.05-2.91)	0.35
Dyslipidemia/ yes	1.33 (0.51-3.50)	0.56
Atrial fibrillation/ yes		
Dialysis/ yes	2.83 (0.30-26.60)	0.36
Rheumatoid arthritis/ yes	0.83 (0.10-6.73)	0.87
Sjögren syndrome/ yes	0.46 (0.13-1.62)	0.22
Scleroderma/ yes	1.24 (0.27-5.78)	0.78
Dermatomyositis/polymyositis/ yes		
MCTD/ yes	1.39 (0.17-11.70)	0.7
eGFR per 1 mL/min/1.73m^2	0.97 (0.95-0.99)	<0.01
Total bilirubin per 1mg/dL	2.62 (1.02-6.74)	<0.05
AST per 1U/L	100 (0.99-1.01)	0.83
ALT per 1U/L	0.99 (0.97-1.02)	0.64
C reactive rotein per 1mg/L	1.23 (0.85-1.79)	0.27
CH 50 per 1/mL	1.03 (0.99-1.07)	0.1
C3 per 1mg/dL	1.00 (0.98-1.02)	0.75
C4 per 1mg/dL	1.01 (0.97-1.06)	0.6
Anti-double stranded DNA IgG antibody/ 1IU/ml	0.99 (0.95-1.02)	0.35
WBC per 1000/uL	1.06 (0.90-1.26)	0.47
Hemoglobin level per 1g/dL	0.87 (0.66-1.13)	0.29
Platelet count per 1000/uL	0.99 (0.98-1.00)	<0.01
Antiphospholipid antibody syndrome/ yes	0.62 (0.17-2.21)	0.46
SLEDAI score/ 1	0.97 (0.90-1.05)	0.49
LAVI per 1ml/m^2	1.04 (1.01-1.08)	<0.01
LVEF per 1%	1.03 (0.93-1.13)	0.59
IVSTd per 1mm	1.28 (1.05-1.56)	<0.05
LVPWTd per 1mm	1.45 (1.09-1.94)	<0.05
E/e' ratio per 1	1.04 (0.98-1.11)	0.18
TRPG per 1mmHg	1.11 (1.05-1.17)	<0.01
RAS inhibitor/ yes	1.14 (0.42-3.09)	0.8
Beta blocker/ yes	6.40 (2.25-18.17)	<0.01
Prednisolone equivalent amount/ 1mg	0.98 (0.92-1.05)	0.63
Immunosuppressant/ yes	0.27 (0.09-0.82)	<0.05
Immunomodulator/ yes	0.53 (0.18-1.50)	0.23

Abbreviations: VHD, valvular heart disease; BP, blood pressure; MCTD, mixed connective tissue disease; eGFR, estimated glomerular filtration rate; DNA, deoxyribo nucleic acid; LAVI, left atrial volume index; IVSTd, interventricular septal thickness in diastole; LVPWTd, left ventricular posterior wall thickness in diastole; LVEF, left ventricular ejection fraction; TRPG, tricuspid regurgitation pressure gradient; RAS, renin angiotensin system; MRA
P value was obtained by the univariate logistic regression analysis model.

4. Discussion

The novel and main findings in the present study were as follows. [1] The morbidity rate of VHD increased with advancing age, [2] a lower platelet count was significantly associated with having VHD, and [3] the use of immunosuppressant therapy might be useful to prevent VHD.

In this study, the prevalence rate of VHD was only 9 % in patients with SLE. Although previous reports have shown huge variations in the rate of VHD [3,28,29], the rate of VHD in the present study was

Table 2b
Multivariate Logistic Regression Analysis for having VHD

	Model 1		Model 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age per 1 year	1.06 (1.02-1.10)	<0.01		
Duration of SLE disease per 1 year	1.04 (0.99-1.10)	0.09		
Body mass index per 1kg/m^2	0.75 (0.62-0.92)	<0.01		
Hypertension/ yes	1.87 (0.57-6.14)	0.30		
LAVI per 1ml/m^2			1.02 (0.99-1.05)	0.18
IVSTd per 1mm			1.15 (0.90-1.47)	0.26
TRPG per 1mmHg			1.08 (1.03-1.14)	<0.01
Platelet count per 1000/uL	0.99 (0.98-1.00)	<0.05	0.99 (0.98-1.00)	<0.05

	Model 3		Model 4		Model 5	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
eGFR per 1mL/min/1.73m2	0.96 (0.94-0.98)	<0.01				
mL/min/1.73m^2	0.98)	01				
Total bilirubin per 1mg/dL	3.06 (1.16-8.07)	<0.05				
Beta blocker/			6.31 (2.09-19.00)	<0.01		
Immunosupperssant/ yes					0.28 (0.09-0.89)	<0.05
Platelet count per 1000/uL	0.99 (0.98-1.00)	<0.01	0.99 (0.98-1.00)	<0.01	0.99 (0.98-1.00)	<0.01

Abbreviations: VHD, valvular heart disease; LAVI, left atrial volume index; IVSTd, interventricular septal thickness in diastole; TRPG, tricuspid regurgitation pressure gradient
p-value was obtained by the logistic regression analysis.
Abbreviations: VHD, valvular heart disease; eGFR, estimated glomerular filtration rate. p-value was obtained by the logistic regression analysis.

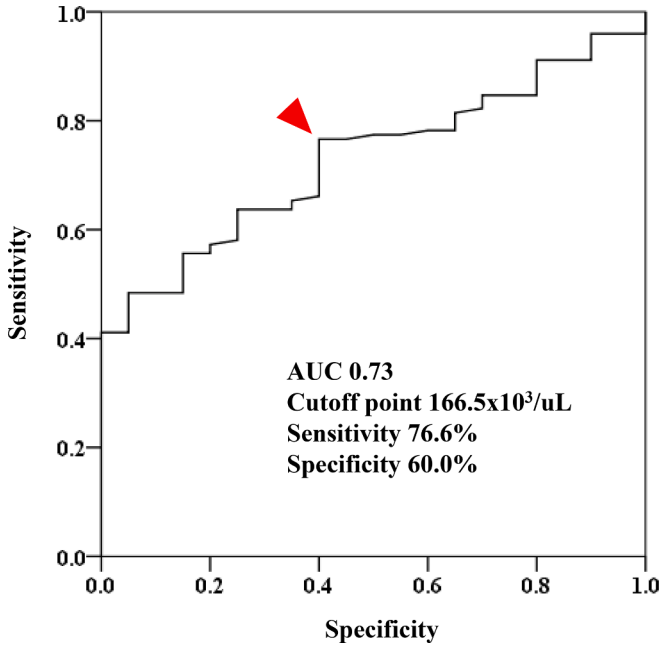

Fig. 2. Receiver operator characteristic curve analysis of platelet count for having valvular heart disease. AUC, area under the curve.

relatively low. The clinical course and survival of SLE have significantly improved because of several factors, including early diagnosis, more accurate use of immunomodulatory drugs, and the advent of new therapies [10–12]. These factors may have contributed to the low rate of VHD in the present study.

Several predictors of VHD were identified in this study. Age was a potent predictor of VHD in the multivariate models. In addition, the prevalence rate of VHD increased with advancing age. The degenerative process of ageing probably increases the susceptibility of injury to the valvular endocardium. The valvulitis and cicatrisation that occur during the disease course may prompt the development of thickening and deformation, resulting in valvular dysfunction in older patients [4].

The present study also revealed that a lower platelet count was significantly and independently associated with having VHD after adjustment for several factors, including ageing. In agreement with the present study, Vivero et al. [30] also showed that thrombocytopaenia was strongly associated with VHD. Thrombocytopaenia is one of the components of the SLEDAI [31], which is an important scoring system used to evaluate the activity of SLE. Therefore, the association between a low platelet count and having VHD might suggest that high SLE activity is an important cause of VHD. However, the SLEDAI itself and other indexes of SLE activity, such as the complement level, white blood cell count, and anti-double-stranded DNA IgG antibody titre, are not associated with VHD. Thus, we considered that a low platelet count alone might not reflect the SLE activity.

APS is an important complication in patients with SLE [32]. Thrombocytopaenia is common in patients with APS and SLE [23]. The formation and deposition of β2-glycoprotein I/antiphospholipid immune complexes can damage valvular surfaces. The classic cardiac lesion of SLE is thought to be Libman–Sacks endocarditis, which manifests as an atypical endocarditis with 1- to 4-mm verrucous vegetations present on each valve. In previous studies, antiphospholipid immune complexes, complement fragments, fibrin, and platelets were found in valvular vegetations from Libman–Sacks endocarditis valve specimens of patients with SLE [33,34]. Therefore, the prevailing theory of SLE-related VHD is that antiphospholipid antibodies contribute to damage via inflammatory- and thrombotic-mediated pathways. However, there was no significant difference between patients with APS and those with VHD in the present study. We excluded two patients with a prosthetic cardiac valve from the logistic regression analysis despite the fact that both of these patients had APS. Cardiac surgical procedures with use of cardiopulmonary bypass are commonly associated with a transient postoperative decrease in the platelet count [35]. Furthermore, implantation of a prosthetic cardiac valve into the circulation alters the haemodynamics and quickly initiates plasmatic and cellular response [14]. Thus, a prosthetic cardiac valve directly induces a decrease in the platelet count, which is why we excluded these two patients with a prosthetic cardiac valve. Because the VHD group comprised only 22 patients, exclusion of these two patients with APS might have attenuated the association between APS and VHD in our data analysis.

In this study, the average platelet count in the VHD group was 162.8 $\times$ 10^3/μL. Therefore, many patients in the VHD group were not diagnosed with thrombocytopaenia. A slight decrease in the platelet count was significantly associated with having VHD, indicating that autoimmune-mediated valvular damage had already occurred when the SLE activity was relatively low and thrombotic complications were not apparent. Because echocardiography is extremely useful for diagnosis of VHD, it is important to perform echocardiography to avoid overlooking VHD when a slight decrease in platelets occurs in patients with SLE.

Another important finding of the present study is that the use of immunosuppressants was significantly associated with the absence of

VHD. Although appropriate immunosuppressive therapy is essential to control SLE disease activity, corticosteroid therapy for Libman–Sacks-related valvular dysfunction reportedly results in increased fibrosis and scarring followed by worsened valvular damage and dysfunction [36,37]. By contrast, several studies have shown that immunosuppressive therapy reduces valve degeneration in patients with Libman–Sacks endocarditis [38,39]. Thus, the present study might indicate the usefulness of immunosuppressive therapy to prevent the progression of VHD.

5. Study limitations

This study has several limitations. First, this was a retrospective single-centre study that included a small number of patients with SLE. This was an important limitation, and further multicentre prospective studies involving more patients are needed to validate our results. Second, we used the SLEDAI as the index of SLE activity. In several patients, however, we could not ascertain the SLEDAI score because there were no data regarding the SLEDAI in their medical records. Third, we did not have information on the precise duration of SLE disease, especially in patients with a long disease duration. This might explain why age, not SLE disease duration, was significantly associated with VHD in the present study.

Despite these limitations, our study uniquely revealed the importance of the platelet count for early diagnosis of VHD in patients with SLE. We believe that our results have important clinical value.

6. Conclusion

The platelet count is useful to predict concomitant VHD in middle-aged and older patients with SLE.

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CRediT authorship contribution statement

Hiroki Usuku: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Eiichiro Yamamoto:** Writing – review & editing. **Komei Sakata:** Writing – review & editing. **Shinya Hirata:** Writing – review & editing. **Ayano Toda:** Formal analysis, Data curation. **Fumi Oike:** Writing – review & editing. **Noriaki Tabata:** Writing – review & editing. **Masanobu Ishii:** Writing – review & editing, Formal analysis. **Shinsuke Hanatani:** Writing – review & editing. **Tadashi Hoshiyama:** Writing – review & editing. **Daisuke Sueta:** Writing – review & editing. **Hisanori Kanazawa:** Writing – review & editing. **Yuichiro Arima:** Writing – review & editing, Conceptualization. **Seiji Takashio:** Writing – review & editing. **Yasushi Matsuzawa:** Writing – review & editing. **Hiroaki Kawano:** Writing – review & editing. **Junichirou Yasunaga:** Writing – review & editing. **Kenichi Tsujita:** Writing – review & editing.

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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Appendix A. Supplementary material

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