Joint effects of uric acid and lymphocyte count on adverse outcomes in elderly patients with rheumatic heart disease undergoing valve replacement surgery

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ABSTRACT

Objectives: Increased uric acid and decreased lymphocyte count are common in elderly patients or those with heart failure, which were prognostic markers. We aimed to investigate the joint effect of uric acid and lymphocyte count for risk stratification in elderly patients with rheumatic heart disease undergoing valve replacement surgery.

Methods: Uric acid to lymphocyte ratio was calculated as serum uric acid (mg/dL)/lymphocyte count ($\times 10^9/L$). Univariate and multivariate analyses were performed to investigate the association of uric acid to lymphocyte ratio, with adverse events in 949 elderly patients with rheumatic heart disease undergoing valve replacement surgery. For clinical use, the uric acid to lymphocyte ratio was classified into 3 groups by the tertile, and a cutoff was also selected according to the receiver operator characteristic curve.

Results: Uric acid to lymphocyte ratio produced relatively higher predictive value (area under the curve, 0.703; 95% confidence interval [CI], 0.630-0.776; $P < .001$) than uric acid or lymphocyte count for in-hospital mortality, and the optimal cutoff was 3.7 (sensitivity, 82.1%; specificity, 52.4%). Uric acid to lymphocyte ratio was an independent predictor for in-hospital (adjusted odds ratio, 1.17; 95% CI, 1.07-1.29; $P = .001$) and 1-year mortality (adjusted hazard ratio, 1.13; 95% CI, 1.03-1.25; $P = .010$). The in-hospital mortality increased from the lowest to the highest uric acid to lymphocyte ratio tertile ($P < .001$) and significantly higher in patients with uric acid to lymphocyte ratio greater than 3.7 ($P < .001$). The cumulative 1-year postoperative mortality risk was significantly higher in patients with uric acid to lymphocyte ratio greater than 3.7 ($P < .001$) or upper uric acid to lymphocyte ratio tertile ($P < .001$).

Conclusions: Uric acid to lymphocyte ratio, combining the effect of uric acid and lymphocyte count, produced more prognostic value in elderly patients with rheumatic heart disease undergoing valve replacement surgery, which could be considered as a preoperative risk-stratified method. (J Thorac Cardio-vasc Surg 2019;158:420-7)

Association of ULR with adverse outcomes.

Central Message

ULR, as a novel index, was independently associated with in-hospital and 1-year mortality in elderly patients with RHD undergoing VRS.

Perspective

ULR combining 2 distinct phenomena—hyperuricemia and reduced lymphocyte count—could be considered as a relatively powerful preoperative risk assessment tool in elderly patients with RHD undergoing VRS. Emphasis should be placed on those patients with pre-VRS high ULR.

See Commentary on page 428.

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Abbreviations and Acronyms

AUC	= area under the curve
CI	= confidence interval
eGFR	= estimated glomerular filtration rate
euroSCORE	= European System for Cardiac Operative Risk Evaluation
HR	= hazard ratio
LVEF	= left ventricular ejection fraction
MACE	= major adverse clinical events
NYHA	= New York Heart Association
OR	= odds ratio
PSP	= pulmonary systolic pressure
RHD	= rheumatic heart disease
ROC	= receiver operating characteristic
RV	= right ventricular
ULR	= uric acid to lymphocyte count ratio
VRS	= valve replacement surgery

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Rheumatic heart disease (RHD) is a chronic acquired heart disease caused by an autoimmune response to group A streptococcal infection, which can lead to valve damage, heart failure, and death.¹ This naturally creates an enormous social and economic burden in developing countries. Valve replacement surgery (VRS) is recommended when symptoms appear in patients with severe valve damage.² However, the early and late postoperative mortality remain high, especially among elderly patients,^{3,4} and few risk-stratified tools were emphasized in this aged population. Therefore, preoperative evaluation is still necessary to identify those patients with a high mortality risk and accordingly make safe and effective clinical decisions to improve prognosis.

Increased uric acid is common in patients with reduced or preserved ejection fraction heart failure, which is due to inflammation, oxidative stress, and cardiorenal syndrome.⁵⁻⁷ Increasing research has shown that hyperuricemia is a predictor for poor outcomes in heart failure.⁸⁻¹⁰ On the other hand, activated neuroendocrine and inflammatory systems in heart failure might decrease the lymphocyte count.¹¹ We hypothesized that uric acid and lymphocyte count can be used in unison to improve the predictive power. Therefore, the present study was designed to evaluate the prognostic role of uric acid to

lymphocyte count ratio (ULR) for adverse outcomes in elderly patients with RHD undergoing VRS.

MATERIALS AND METHODS**Subjects**

The study was retrospectively conducted in consecutive patients with RHD undergoing VRS. A total of 1115 elderly patients (age ≥ 60 years) were recruited in the Guangdong General Hospital from March 2009 to December 2015. All patients received at least 1 valve replacement. The exclusion criteria were as follows: (1) age less than 60 years; (2) history of malignant tumor; (3) previous diagnosis of gout; and (4) missed preoperative serum uric acid or lymphocyte count records. This study was approved by the Ethics Committee of our hospital with a waiver of informed consent because of the retrospective study design. Oral informed consent was obtained from patients or their relatives by telephone and recorded by trained nurses during the follow-up period.

Examination and Data Collection

Blood count and other variables, such as serum creatinine and electrolyte levels, were analyzed during hospital admission. Uric acid and other standard clinical parameters were routinely measured on the morning of the first day after admission in our center. Uric acid was automatically detected by the Beckman Coulter AU5800 (Beckman Coulter Inc, Brea, Calif), and lymphocyte count was measured by the impedance method using an automated blood cell counter (XE-5000, Sysmex, Kobe, Japan). ULR was calculated as follows: serum uric acid (mg/dL)/lymphocyte count ($\times 10^9/L$). Transthoracic echocardiography was routinely performed before surgery, and left ventricular end-diastolic dimension, right ventricular (RV) diameter, left ventricular ejection fraction (LVEF), pulmonary systolic pressure (PSP), and other parameters were recorded.

Clinical information was collected from an electronic case report form by 1 researcher and randomly confirmed by another researcher. The European System for Cardiac Operative Risk Evaluation (euroSCORE) was calculated according to the criteria in this analysis.¹²

Follow-up and End Points

After discharge, surviving patients were followed up by telephone interview, examination of readmission clinical records, and outpatient clinic interviews. The primary end point was in-hospital death. One-year postoperative mortality and in-hospital major adverse clinical events (MACE), including dialysis, stroke, or death, were considered as the secondary end points. The incidence of postoperative acute renal failure was also recorded, which was defined according to RIFLE criteria¹³ as an increase in serum creatinine to more than 3-fold from baseline, an increase in serum creatinine to more than $354 \mu\text{mol/L}$, or an acute increase of at least $44 \mu\text{mol/L}$.

Statistical Analysis

The SPSS program (SPSS Inc, Chicago, Ill) was used for all analyses. The results are presented as means ($\pm$ standard deviation) for continuous variables or percentages for categorical variables. The chi-square or Fisher exact test was used to compare categorical variables and variance or Wilcoxon rank-sum test to compare continuous variables. Cumulative rate of 1-year mortality was shown using Kaplan–Meier curves and compared using the log-rank test. Univariate and multivariable logistic regression analyses and Cox survival models were carried out to explore the relationship of variables with in-hospital and 1-year mortality, respectively. All significant variables in the univariate analysis were included in the multivariable model.

The bootstrap method with 1000 replications was used to perform an internal cross-validation of the ULR. The optimal cut-off was evaluated by receiver operator characteristic (ROC) curve and the average of area under the curve (AUC) was reported. The AUC was compared using the nonparametric approach of DeLong and colleagues.¹⁴

FIGURE 1. Patient disposition and selection of study cohort. ULR, Uric acid to lymphocyte count ratio; AKI, acute kidney injury; MACE, major adverse clinical events.

RESULTS

All Patients

There were 1115 elderly patients with RHD who underwent VRS in our database, among whom 949 were finally included per our predefined exclusion criteria (Figure 1). The mean $\pm$ standard deviation age of the whole cohort was 64 ± 4 years, and 64.7% of patients were female. During the hospital stay, 56 patients (5.9%) died (cardiac death in 41), 19 patients (2.0%) had a stroke, and 46 patients (4.8%) received dialysis treatment.

Development and Validation of Uric Acid to Lymphocyte Count Ratio

An ROC curve analysis was conducted to determine the predictive value of uric acid, lymphocyte count, the combination by including both uric acid and lymphocyte count in the logistic model (the linear combination predictor), and ULR for in-hospital death. When compared with uric acid (AUC, 0.668; 95% confidence interval [CI], 0.590-0.746; $P < .001$) (Figure 2) and lymphocyte count (AUC, 0.637; 95% CI, 0.555-0.719; $P = .001$) (Figure 2), ULR (AUC, 0.703; 95% CI, 0.630-0.776; $P < .001$) (Figure 2) showed a higher predictive value for in-hospital mortality (compared with uric acid and lymphocyte count: $P = .334$ and $.030$, respectively), although it was not significant when compared with uric acid. The ULR also had a similar

FIGURE 2. ROC curves of ULR, uric acid, lymphocyte count, and the prediction score developed by including the uric acid and lymphocyte count in the logistic model for in-hospital mortality. AUC, Area under the curve; CI, confidence interval; ULR, uric acid to lymphocyte count ratio.

AUC with the linear combination predictor (AUC, 0.709; 95% CI, 0.636-0.783; $P < .001$) (Figure 2), but, for easier clinical use, we preferred the ULR. The bootstrapping internal validation for the ULR yielded an average AUC of 0.704 (95% CI, 0.640-0.763) and was calibrated with a Hosmer–Lemeshow chi-square statistic of 12.839 ($P = .118$).

We also compared ULR with the EuroSCORE in 903 patients with available EuroSCORE. ULR showed an insignificantly higher predictive ability than the EuroSCORE (AUC, 0.701 vs 0.629, $P = .141$) (Figure E1).

Uric Acid to Lymphocyte Count Ratio and Clinical Characteristics

Included patients were stratified into 3 groups by the tertile of ULR: less than 3.1 (n = 319), 3.1 to 4.4 (n = 312), and 4.4 or greater (n = 318). Table 1 shows the baseline clinical characteristics of included patients. Patients in the first ULR tertile were significantly younger (63.7 ± 3.3 years vs 64.2 ± 3.5 years vs 64.5 ± 4.0 years, $P = .028$). Patients with a higher ULR were more likely to be male. A positive trend with the proportion of New York Heart Association (NYHA) class III and IV, anemia, serum creatinine, uric acid, and C-reactive protein was

TABLE 1. Baseline characteristics stratified by tertile of uric acid to lymphocyte count ratio

Clinical variables	First ULR tertile (<3.1 , n = 319)	Second ULR tertile ($3.1-4.4$, n = 312)	Third ULR tertile (≥ 4.4 , n = 318)	P value
Age (y)	63.7 $\pm$ 3.3	64.2 $\pm$ 3.5	64.5 $\pm$ 4.0	.028
Women, n (%)	241 (75.5)	195 (62.5)	178 (56.0)	<.001
Concomitant disorders, n (%)				
Diabetes mellitus	21 (6.6)	31 (9.9)	34 (10.7)	.158
Hypertension	54 (16.9)	64 (20.5)	70 (22.0)	.255
NYHA class III-IV, n (%)	118 (37.0)	130 (41.7)	160 (50.3)	.003
Serum creatinine ($\mu\text{mol/L}$)	74.3 $\pm$ 18.4	82.7 $\pm$ 27.5	94.5 $\pm$ 32.1	<.001
WBC count ($\times 10^9/\text{L}$)	7.2 $\pm$ 1.9	6.6 $\pm$ 1.7	6.3 $\pm$ 1.7	<.001
Neutrophil count ($\times 10^9/\text{L}$)	3.9 $\pm$ 1.5	3.9 $\pm$ 1.4	4.0 $\pm$ 1.5	.256
Lymphocyte count ($\times 10^9/\text{L}$)	2.5 $\pm$ 0.6	2.0 $\pm$ 0.4	1.4 $\pm$ 0.4	<.001
Hemoglobin (g/L)	134.5 $\pm$ 14.0	132.1 $\pm$ 17.1	130.1 $\pm$ 17.5	.003
Anemia, n (%)	19 (6.0)	33 (10.6)	50 (15.7)	<.001
Uric acid (mg/dL)	5.9 $\pm$ 1.4	7.2 $\pm$ 1.5	8.7 $\pm$ 2.1	<.001
CRP (mg/L)	2.5 (1.7-4.3)	2.8 (1.8-5.4)	3.7 (2.1-6.3)	<.001
LVEDD (mm)	48.4 $\pm$ 7.6	48.8 $\pm$ 8.3	50.4 $\pm$ 9.7	.014
RV diameter (mm)	50.0 $\pm$ 5.8	51.1 $\pm$ 6.2	54.0 $\pm$ 7.9	<.001
LVEF (%)	62.8 $\pm$ 8.1	62.6 $\pm$ 8.7	60.0 $\pm$ 10.3	<.001
PSP (mm Hg)	39.4 $\pm$ 14.0	44.9 $\pm$ 19.5	50.6 $\pm$ 20.3	<.001
Valve surgery				
AVR	139 (43.6)	144 (46.2)	163 (51.3)	.142
MVR	295 (92.5)	290 (92.9)	303 (95.3)	.303
TVI	223 (69.9)	228 (73.1)	262 (82.4)	.001
AVR + MVR	116 (36.4)	124 (39.7)	153 (48.1)	.008
AVR + MVR + TVI	89 (27.9)	97 (31.1)	124 (39.0)	.009
CABG surgery	22 (6.9)	29 (9.3)	19 (6.0)	.259
EuroSCORE	4.4 $\pm$ 1.0	4.5 $\pm$ 1.2	5.0 $\pm$ 1.5	<.001
Postoperative renal failure	130 (40.8)	148 (47.6)	170 (53.6)	.005

ULR, Uric acid to lymphocyte count ratio; NYHA, New York Heart Association; WBC, white blood cell; CRP, C-reactive protein; LVEDD, left ventricular end-diastolic dimension; RV, right ventricular; LVEF, left ventricular ejection fraction; PSP, pulmonary systolic pressure; AVR, aortic valve replacement; MVR, mitral valve replacement; TVI, tricuspid valve intervention; CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

observed with increasing ULR. However, a negative trend with white blood cell count, lymphocyte count, hemoglobin, and LVEF was observed with increasing ULR. Higher left ventricular end-diastolic dimension, RV diameter, and PSP were found in patients in the upper tertile. In addition, there was a trend among tertiles toward a higher incidence of tricuspid valve intervention as ULR increased. The data for assessing postoperative renal failure were available in 947 patients. The incidence of postoperative renal failure was 47.3% (448/947), which is significantly higher in patients in the upper tertile (40.8% vs 47.6% vs 53.6%, $P = .005$) (Table 1).

Uric Acid to Lymphocyte Count Ratio and In-Hospital Clinical Outcomes

The risk factors for in-hospital death according to univariate and multivariate logistic regression analyses are

presented in Table 2. The univariate analysis revealed that male patients and patients with a high ULR, older age, a high proportion of NYHA class III and IV, estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m², anemia, a high RV diameter, a high PSP, and low LVEF were at higher risk for in-hospital death. In the multivariate analysis, ULR was the only significant independent indicator for in-hospital death (odds ratio [OR], 1.17; 95% CI, 1.07-1.29; $P = .001$).

Uric Acid to Lymphocyte Count Ratio and One-Year Postoperative Mortality

Patients were followed up for 1 year after VRS. In this time, 69 patients died and 88 patients were lost to follow-up. In univariate Cox proportional hazards analysis, ULR was significantly associated with 1-year postoperative mortality (unadjusted hazard ratio [HR], 1.19; $P < .001$,

TABLE 2. Results of logistic regression analysis for in-hospital mortality

Clinical variables	Univariate		Multivariate	
	OR	P	OR (95% CI)	P
ULR	1.24	<.001	1.17 (1.07-1.29)	.001
Age (y)	1.08	.019	1.06 (0.98-1.13)	.144
Women	0.57	.039	0.73 (0.40-1.32)	.296
Diabetes mellitus	1.22	.658		
Hypertension	0.76	.470		
NYHA class III-IV	2.32	.003	1.62 (0.90-2.93)	.110
eGFR <60 mL/min/1.73 m ²	2.15	.010	1.14 (0.57-2.27)	.707
WBC count	0.93	.352		
Neutrophil count	1.03	.732		
Anemia	2.73	.003	1.60 (0.77-3.32)	.206
Log ₁₀ CRP	1.75	.093		
LVEDD	1.02	.227		
RV diameter	1.06	<.001	1.01 (0.97-1.05)	.710
LVEF	0.97	.016	0.98 (0.95-1.01)	.129
PSP	1.02	<.001	1.02 (1.00-1.03)	.046
AVR	1.23	.460		
MVR	0.89	.822		
TVI	1.56	.214		
AVR + MVR	1.24	.433		
AVR + MVR + TVI	1.06	.835		
CABG surgery	1.55	.328		

OR, Odds ratio; CI, confidence interval; ULR, uric acid to lymphocyte count ratio; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; WBC, white blood cell; CRP, C-reactive protein; LVEDD, left ventricular end-diastolic dimension; RV, right ventricular; LVEF, left ventricular ejection fraction; PSP, pulmonary systolic pressure; AVR, aortic valve replacement; MVR, mitral valve replacement; TVI, tricuspid valve intervention; CABG, coronary artery bypass grafting.

Table 3). Other significant parameters included age, sex, NYHA class III and IV, eGFR less than 60 mL/min/1.73 m², anemia, log₁₀ C-reactive protein, RV diameter, LVEF, and PSP. After adjusting for these potential risk factors, ULR remained as the only independent predictor for 1-year postoperative death (adjusted HR, 1.13; 95% CI, 1.03-1.25; $P = .010$) (Table 3).

Clinical Application of Uric Acid to Lymphocyte Count Ratio

We arbitrarily categorized the risk scores into 3 groups by the tertile of ULR to enhance its clinical use: low risk, moderate risk, and high risk. The in-hospital mortality (2.2% vs 4.8% vs 10.7%, $P < .001$) (Figure 3, A), MACE (3.4% vs 8.0% vs 13.2%, $P < .001$) (Figure 3, A), and 1-year mortality (2.2% vs 6.4% vs 13.2%, $P < .001$) (Figure 3, A) increased from the lowest to the highest ULR tertile. Compared with the first ULR tertile, the third ULR tertile

TABLE 3. Results of Cox proportional hazards model for postoperative 1-year mortality

Clinical variables	Univariate		Multivariate	
	HR	P	HR (95% CI)	P
ULR	1.19	<.001	1.13 (1.03-1.25)	.010
Age (y)	1.07	.030	1.02 (0.96-1.10)	.505
Women	0.53	.009	0.71 (0.41-1.21)	.209
Diabetes mellitus	1.11	.789		
Hypertension	0.68	.254		
NYHA class III-IV	1.92	.007	1.17 (0.69-1.97)	.564
eGFR <60 mL/min/1.73 m ²	2.12	.004	1.07 (0.58-1.98)	.839
WBC count	0.97	.683		
Neutrophil count	1.09	.258		
Anemia	2.61	.001	1.91 (1.02-3.58)	.044
Log ₁₀ CRP	1.98	.014	0.99 (0.55-1.78)	.962
LVEDD	1.02	.176		
RV diameter	1.07	<.001	1.02 (0.98-1.06)	.365
LVEF	0.96	.001	0.99 (0.96-1.02)	.389
PSP	1.02	<.001	1.01 (1.00-1.03)	.032
AVR	1.33	.243		
MVR	0.73	.457		
TVI	1.29	.389		
AVR + MVR	1.25	.365		
AVR + MVR + TVI	1.03	.909		
CABG surgery	1.45	.351		

HR, Hazard ratio; CI, confidence interval; ULR, uric acid to lymphocyte count ratio; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; WBC, white blood cell; CRP, C-reactive protein; LVEDD, left ventricular end-diastolic dimension; RV, right ventricular; LVEF, left ventricular ejection fraction; PSP, pulmonary systolic pressure; AVR, aortic valve replacement; MVR, mitral valve replacement; TVI, tricuspid valve intervention; CABG, coronary artery bypass grafting.

was an independent predictor for in-hospital mortality (adjusted OR, 2.71; 95% CI, 1.10-6.66; $P = .030$) (Table E1) and 1-year mortality (adjusted HR, 2.98; 95% CI, 1.25-7.09; $P = .014$) (Table E1). Compared with low-risk patients, the cumulative 1-year postoperative mortality risk was significantly higher in moderate-risk and high-risk patients (log-rank = 30.21, $P < .001$) (Figure 4, A).

In addition, we also divided the patients into 2 risk levels using a cutoff of 3.7 (sensitivity 82.1%; specificity 52.4%) selected according to the ROC curve. The in-hospital mortality (2.3% vs 9.6%, $P < .001$) (Figure 3, B), MACE (4.2% vs 12.4%, $P < .001$) (Figure 3, B), and 1-year mortality (2.7% vs 11.9%, $P < .001$) (Figure 3, B) were significantly higher in patients with ULR greater than 3.7. ULR greater than 3.7 was independently associated with in-hospital (adjusted OR, 2.69; 95% CI, 1.30-5.56; $P = .007$, Table E1) and 1-year mortality (adjusted HR, 2.52; 95% CI, 1.30-4.87; $P = .006$) (Table E1). Patients with ULR greater

FIGURE 3. Prevalence of adverse events. *MACE*, Major adverse clinical events; *ULR*, uric acid to lymphocyte count ratio.

than 3.7 had worse 1-year prognosis than those without (log-rank = 31.15, $P < .001$) (Figure 4, B).

DISCUSSION

To our best knowledge, this study was the first to use ULR as a preoperative risk-stratified method. We found that ULR produced relatively higher prognostic value than uric acid or lymphocyte count, and was independently associated with in-hospital and 1-year mortality in elderly patients with RHD undergoing VRS. In addition, the predictive ability of ULR was similar to the EuroSCORE. The use of ULR could provide prognostic information for early and fast preoperative risk assessment in elderly patients with RHD undergoing VRS.

In this study, 949 elderly patients with RHD were retrospectively analyzed, and all underwent at least 1 VRS because of severe valve damage with symptoms of cardiac dysfunction. Oxidative stress, which triggered by activating the sympathetic nervous and the renin-angiotensin-aldosterone system, played a critical role in the

pathophysiology of heart failure.^{15,16} In this condition, reactive oxygen species including xanthine oxidase were excessively produced. Xanthine oxidase is an important catalyzing enzyme, which induced the formation of uric acid from xanthine and hypoxanthine.¹⁷ In addition, uric acid would be released in hypoxic conditions.¹⁸ Hyperuricemia might be due to hypoxia and impaired oxidative metabolism in heart failure. A decrease in renal perfusion in heart failure was another mechanism for increasing serum uric acid levels. Uric acid is primarily excreted through the kidney. More than 50% of patients with acute and chronic heart failure have renal dysfunction.¹⁹ In our study, 74.1% of included patients had existing renal insufficiency (eGFR <90 mL/min/1.73 m²). Decline in cardiac output, activation of neurohormonal systems, or inflammation in heart failure contributed to impaired renal function, which subsequently diminished the excretion of uric acid.²⁰ Hyperuricemia was a marker of excessive oxidative stress and severity of renal dysfunction, which was established as a predictor for adverse prognosis in several conditions.²¹⁻²³ Inflammation also involved the pathogenesis and progression of heart failure.^{24,25} Uric acid increased in keeping with the level of inflammatory markers in chronic heart failure, which represented the severity of cardiac dysfunction.⁷

Decreased lymphocyte count was another phenomenon in patients with heart failure because of increased neurohormonal activation. Increased cortisol and catecholamines were postulated to be the underlying mechanism causing lymphopenia by triggering apoptosis and downregulating the proliferation and differentiation of lymphocytes.^{26,27} In addition, RHD is an autoimmune disease and inflammatory response still persists in its chronic phase.²⁸ Further, inflammation and immune response were important elements in the pathogenesis and progression of heart failure.²⁹ The over-release of proinflammatory cytokines may be directly related to lowered lymphocyte counts.³⁰ Another possible mechanism was intestinal lymphangiectasia, which is caused by systemic venous and lymphatic hypertension. This lymphangiectasia triggered loss of lymphocyte-rich lymph into the gastrointestinal tract, resulting in lymphopenia.

In this study, we only focused on elderly patients, whose organ function had declined with age. Few preoperative risk-stratified methods were emphasized in this special population. Epidemiologic data revealed that the prevalence of chronic kidney disease in the elderly is estimated to be 40%.³¹ This renal dysfunction contributed to hyperuricemia. On the other hand, reduced lymphocyte count and its function were common in elderly patients and mostly depend on nutritional status.^{32,33} Hyperuricemia and reduced lymphocyte count were established predictors for poor outcomes in heart failure.^{8,34} These mechanisms encouraged us to combine these 2 parameters into a new

FIGURE 4. Cumulative incidence curve for 1-year postoperative death. A, Classified by the tertiles of ULR. B, Classified by the receiver operating characteristic curve selected cut-off of ULR. ULR, Uric acid to lymphocyte count ratio.

variable as a preoperative risk-evaluated method in elderly patients with RHD undergoing VRS. The ULR appeared to be a more powerful predictor than either parameter alone, which could identify more patients at high risk of postoperative death.

Study Limitations

Our study has a few limitations. First, although a multivariate analysis was performed to adjust the potential confounding factors, some residual factors might have had an impact on the end points because of the retrospective study design. Second, we did not investigate the reasons for preoperative hyperuricemia and reduced lymphocyte count. However, this study aimed to identify a novel marker and its prognostic value in elderly patients with RHD undergoing VRS. Third, ULR had a higher ability than uric acid for predicting in-hospital death, but it did not reach statistical significance probably because of the small sample size. In

the later study, we will continue to increase the sample size to determine whether ULR is more powerful than uric acid. Finally, the effect of ULR was explored only in elderly patients. Whether it can be extrapolated to other age groups in the population remains to be seen.

CONCLUSIONS

To our best knowledge, this study was the first to combine 2 distinct phenomena—hyperuricemia and reduced lymphocyte count—to predict adverse prognosis among elderly patients with RHD undergoing VRS. This novel index, ULR, produced relatively higher predictive power and was independently associated with in-hospital and 1-year mortality, which could be considered as an early and fast preoperative risk assessment tool. Emphasis should be placed on those elderly patients with RHD and preoperative high ULR (Video 1).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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VIDEO 1. The importance and relevance of the article are explained. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32817-4/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32817-4/fulltext).

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Key Words: lymphocyte, outcomes, rheumatic heart disease, uric acid, valve replacement surgery

FIGURE E1. ROC curves of ULR and euroSCORE for in-hospital mortality (data for euroSCORE missed for 46 patients). *ULR*, Uric acid to lymphocyte count ratio; *AUC*, area under the curve; *CI*, confidence interval; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation.

TABLE E1. Multivariable analysis for in-hospital and 1-year death

Variable	ULR					
	Second vs first tertile	<i>P</i>	Third vs first tertile	<i>P</i>	>3.7 vs ≤3.7	<i>P</i>
In-hospital death						
Unadjusted OR (95% CI)	2.25 (0.91-5.60)	.081	5.34 (2.33-12.23)	<.001	4.53 (2.31-8.86)	<.001
Adjusted OR (95% CI)*	1.70 (0.67-4.31)	.264	2.71 (1.10-6.66)	.030	2.69 (1.30-5.56)	.007
1-y death						
Unadjusted HR (95% CI)	3.08 (1.30-7.29)	.010	6.56 (2.95-14.59)	<.001	4.74 (2.59-8.67)	<.001
Adjusted HR (95% CI)†	2.30 (0.95-5.54)	.064	2.98 (1.25-7.09)	.014	2.52 (1.30-4.87)	.006

ULR, Uric acid to lymphocyte count ratio; *OR*, odds ratio; *CI*, confidence interval; *HR*, hazard ratio. *Adjusted for age, sex, NYHA class III-IV, eGFR less than 60 mL/min/1.73 m², anemia, RV diameter, LVEF, and PSP. †Adjusted for age, sex, NYHA class III and IV, eGFR less than 60 mL/min/1.73 m², anemia, log₁₀ CRP, RV diameter, LVEF, and PSP.