中文題目：嚴重慢性主動脈瓣逆流在亞洲族群的種族差異性之多國多中心研究

英文題目：Inter-ethnic differences in Asian patients with chronic aortic regurgitation: a multicenter outcome study

作　　者：蕭擎宇，李建璋，蔡婕玫，羅皓允，許榮彬，陳益祥，高憲立，林亮宇，陳文鍾，何奕倫，竹內正明，和泉千里，楊荔丹

服務單位：[1]台灣大學附設醫院內科部，[2]國立台灣大學醫學系，[3]日本大阪國立心臟腦血管中心心血管內科部，[4]日本北九州職業與環境衛生大學附設醫院檢驗與輸血醫學部

Background:

Chronic hemodynamically-significant aortic regurgitation (AR) exhibited excess risk of death, yet Asian data remains largely unexplored. Most physicians abide by European or US valvular heart disease guidelines because most of the clinical evidence were from studies conducted in western countries and Asian data is scarce.

The cutoffs of absolute left ventricular (LV) size─ a LV end-systolic dimension (LVESD) of 50mm and a LV end-diastolic dimension (LVEDD) of 65mm─may fall short since Asian people have uniquely smaller body surface area than Caucasians. We also recently found that inter-ethnic differences existed in patients with AR in a cross-sectional study.

In Japanese and Taiwanese population with hemodynamically-significant AR, we sought to: (1) explore inter-ethnic differences in clinical presentation, (2) identify LV parameters and the cutoffs informing risks of death, and (3) explore the impact of aortic valve surgery (AVS).

Methods:

We included 1259 consecutive patients with ≥moderate-severe AR between 2008 to 2020 from 3 tertiary referral hospitals (National Taiwan University Hospital, National Cerebral and Cardiovascular Center, Osaka, Japan, and University of Occupational and Environmental Health, Kitakyushu, Japan) in Taiwan and Japan.

Their baseline transthoracic echocardiography was de novo reviewed. LV volumes were derived from biplane disk-summation method or single plane if biplane not feasible. Other chamber quantification, and semi-quantitative measurements for AR (vena contracta width, pressure half-time) were performed.

Surgical indications for AVS were stratified based on both 2017 European Society of Cardiology and 2014 American College of Cardiology guidelines, including 1) symptoms, 2) LV

ejection fraction (LVEF) ≤ 50%, 3) LVESD >50 mm or indexed LVESD(LVESDi) >25 mm/m^2 , 4) surgery for aortic dilatation/aneurysms and 5) LVEDD>65mm.

Our primary endpoint was all-cause death (ACD). The secondary endpoint was cardiovascular death (CVD). Observation time was either 1) between baseline transthoracic echo (TTE) and death, or last follow-up (total follow-up) or 2) between baseline TTE and death, time of AVS or last follow-up (death under medical surveillance).

Results:

There were 744 (59%) Taiwanese (64±17 years) and 515 (41%) Japanese (65±17 years) participants, respectively.

As compared to Taiwanese, Japanese were less symptomatic (48% vs 38%), had smaller body surface area (1.7±0.2m^2 vs 1.6±0.2m^2), lower Charlson index (1[interquartile-range (IQR): 0-2] vs 0[IQR: 0-2]), more AVS (35% vs 44%), larger indexed left ventricular end-systolic dimension (LVESDi), and indexed LV end-systolic volume (LVESVi), all P <0.01 (**Table 1**).

At a median follow-up of 4.1(IQR: 1.5-7.2) years, 240(19%) patients died (201 deaths under medical management and 39 deaths after AVS). Overall, Japanese AR patients had better survival than Taiwanese counterpart. Ten-year survival in Japanese and Taiwanese was 84±3% and 64±2%, respectively (P<0.0001); Taiwanese had 2.19-fold and 2.45-fold risk of death without and with adjustment for age and sex, respectively (P<0.0001).

Aortic valve surgery was associated with reduced ACD noted in the entire, Taiwanese and Japanese cohort. After adjusting for covariates, LVEF, LVESDi, and LVESVi were all associated with death under medical surveillance (all P<0.001) in Taiwanese; in Japanese, only LVEF (hazard ratio [HR] per 10%, 0.72; P=0.033) was associated. However, all 3 LV parameters were determinants for CVD in both Japanese and Taiwanese (all P≤0.04) (**Table 2**).

Spline curves showed that continuous risks of cardiovascular death started to rise in Taiwanese with LVEF ≤57%, LVESDi ≥22 mm/m^2, LVESVi ≥40mL/m^2; the corresponding cutoffs in Japanese were LVEF ≤50%, LVESDi ≥25mm/m^2, and LVESVi ≥48mL/m^2 (**Figure 1, Figure 2**).

Conclusions:

In this multicenter Asian-cohort of patients with hemodynamically-significant AR, we report for the first time the presentation, survival and cutoffs for 3 LV parameters informing risks of death. Interethnic differences between Taiwanese and Japanese were identified. Compared to Taiwanese, Japanese population exhibited a higher overall survival, which reflected on the higher cutoffs of LVESDi and LVESVi for death. The threshold informing increased risk of

death for LVEF, LVESDi and LVESVi in Taiwanese was similar to western-population, and in Japanese, they were slightly different.

Overall, risk of death started to rise once LVEF ≤ 55-56% for ACD and 50-57% for CVD. Thus, contemporary data, regardless of East and West, seemed to suggest that LVEF 55% is a reasonable cutoff for timely surgical referral. The cutoff of LVESDi 22mm/m^2 from Taiwanese was similar to the western population; this finding helps generalize the results conducted in western studies. It also highlights the importance of using indexed LV-parameters as a common communication language in patients with valvular heart disease and small stature. LVESVi cutoff of 40ml/m^2 from Taiwanese was also similar to the western population; although this parameter was not yet integrated into current guidelines for management of patients with AR due to insufficient evidence, our results may serve as a red flag and risk-stratification tool for clinicians.

Finally, our study findings provide evidence for future guideline amendment and guidance when treating Asian patients or patients with Asian ancestry in the rest of the world.

Table 1. Baseline characteristics

	Total N=1259	**Taiwan** N=744	**Japan** N=515	**P**
Age, year	64±17	64±17	65±17	0.20
Female	325(26)	169(23)	156(30)	**0.002**
Body surface area, m^2	1.67±0.21	1.70±0.20	1.61±0.21	**<.0001**
Body mass index, kg/m^2	23.0±4.0	23.6±3.9	22.3±4.1	
Systolic blood pressure, mmHg	135±20	135±18	136±22	0.49
Diastolic blood pressure, mmHg	65±13	66±12	64±13	**0.0019**
Pulse pressure, mmHg	70±20	69±20	72±20	**0.006**
Heart rate, bpm	70±13	71±13	67±13	**<.0001**
Hypertension	784(63)	453(61)	331(64)	0.28
Hyperlipidemia	273(22)	131(18)	142(28)	**<.0001**
Diabetes mellitus	102(8)	58(8)	44(9)	0.65
Connective tissue disease	95(8)	47(6)	48(9)	0.05
Coronary artery disease	203(16)	175(24)	28(5)	**<.0001**
Charlson comorbidity index	1(0-2)	1(0-2)	0(0-2)	**0.0001**
NYHA functional class (n=1245)				**0.002**
I*	700(56)	381(52)	319(62)	
II	418(34)	267(37)	151(29)	
III+IV	127(10)	83(11)	44(9)	
BAV	243(19)	150(20)	93(18)	0.35
BAV fusion type‡				0.31
RL	177(73)	108(72)	69(74)	
RN	50(21)	34(23)	16(17)	
LN	15(6)	7(5)	8(9)	
LVEF via Simpson method	55±11	58±10	52±11	**<0.0001**
LVEDD, mm	60±8	60±7	61±8	**0.001**
LVEDDi, mm/m^2	36.6±5.2	35.4±4.7	38.2±5.4	**<.0001**
LVESD, mm	41±9	39±8	43±9	**<.0001**
LVESDi, mm/m^2	24.7±5.7	22.9±4.8	27.0±5.9	**<.0001**
LVESDi>25 mm/m^2	481(38)	186(25)	295(57)	**<.0001**
LVEDVi, ml/m^2 (n=1247)	108±39	99.3±36.9	120.5±39.3	**<.0001**
LVESVi, ml/m^2 (n=1245)	50±28	43.4±23.8	59.4±30.8	**<.0001**
LAVi, ml/m^2 (n=1212)	38±17	31.3±12.7	46.4±18.9	**<.0001**
E/e' (n=990)	13±6	14±6	12±6	**<.0001**

RVSP (n=1138)	30±10	31±10	30±9	0.06
Atrial fibrillation (n=1257)	96(8)	52(7)	44(9)	0.31
AR vena contracta (n=1073)	6.6±1.7	7.0±1.9	6.1±1.3	**<.0001**
AR EROA (n=455)	0.28±0.10	—	0.28±0.10	—
AR Regurgitant volume (n=455)	61±17	—	61±17	—
AR pressure half time	380±104	349±110	387±101	**0.001**
Aorta dimensions				
Annulus, mm (n=1232)	23.4±3.2	23.4±3.3	23.4±2.8	0.76
Indexed annulus (n=1232)	14.2±1.9	13.9±1.9	14.6±1.9	**<.0001**
Sinus of Valsalva, mm (n=1231)	40.5±8.2	41.6±8.4	39.0±7.7	**<.0001**
Indexed Sinus of Valsalva (n=1231)	24.4±4.9	24.5±4.9	24.3±4.8	0.50
Mid-ascending aorta, mm (n=879)	40.4±8.1	44.2±8.1	37.7±7.1	**<.0001**
Indexed mid-ascending aorta(n=879)	24.7±5.5	26.1±5.3	23.7±5.3	**<.0001**
Surgery parameters				
AV surgery	483(38)	258(35)	225(44)	**0.001**
Surgery and Surgical indications*(n=481)				**<.0001**
Symptoms	285(59)	198(77)	87(39)	
LVEF<50%	47(10)	2(<1)	45(20)	
LVESD(i)>50mm(25mm/m^2)	75(16)	24(9)	51(23)	
Aortic aneurysm	21(4)	14(5)	7(3)	
LVEDD>65mm	36(7)	10(4)	26(12)	
Early surgery	17(4)	10(4)	7(3)	
Aortic valve repair	24(5)	8(3)	16(7)	**0.04**
Bioprosthesis (n=457)	330(72)	167(67)	163(78)	**0.006**
Concomitant aorta surgery(n=481)†	170(35)	115(45)	55(25)	**<.0001**
Concomitant CABG	48(10)	29(11)	19(9)	0.31

Values are mean±standard deviations, n (%), or median (interquartile range).
AV, aortic valve; AR, aortic regurgitation; BAV, bicuspid aortic valve; CABG, coronary artery bypass grafting; EF, ejection fraction; EDD, end-diastolic dimension; ESD(i), end-systolic dimension (index); EDV, end-diastolic volume; ESV, end-systolic volume; E/e', peak mitral inflow velocity to early diastolic mitral annular velocity ratio; EROA, effective regurgitant orifice area; LN, left-noncoronary cusp fusion; LV, left ventricular; LAVi, left atrial volume index; NYHA, New York Heart Association; RL, right-left coronary cusp fusion; RN, right-noncoronary cusp fusion; RVSP, right ventricular systolic pressure.
‡Exclude 1 patient with unknown phenotype.

*2 received surgery elsewhere had unknown surgical indications thus excluded from analysis
† Excluding 2 patients

Table 2. Multivariate Cox analysis for predictors of all-cause death under medical surveillance (201 deaths)*

	Total, n=1259		Taiwan, n=744		Japan, n=515	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Model 1: LVEF						
Age	1.06(1.05-1.08)	**<0.0001**	1.06(1.05-1.08)	**<0.0001**	1.06(1.02-1.10)	**<.0001**
Female	1.24(0.92-1.69)	0.15	1.45(1.02-2.05)	**0.04**	1.56(0.80-3.06)	0.19
Charlson comorbidity index	1.28(1.20-1.37)	**<0.0001**	1.20(1.11-1.30)	**<0.0001**	1.43(1.25-1.64)	**<0.0001**
NYHA (I as reference)						
II	1.10(0.79-1.53)	0.56	1.10(0.76-1.61)	0.59		
III/IV	2.04(1.31-3.17)	**0.001**	2.12(1.26-3.57)	**0.004**		
LVEF per 10%	0.88(0.78-1.01)	0.07	0.82(0.71-0.96)	**0.016**	0.72(0.55-0.97)	**0.033**
Model 2: LVESDi†						
Age	1.06(1.05-1.08)	**<0.0001**	1.06(1.04-1.08)	**<0.0001**	1.06(1.02-1.10)	**0.0004**
Female	1.20(0.89-1.63)	0.21	1.35(0.95-1.91)	0.08	1.36(0.70-2.64)	0.35
Charlson comorbidity index	1.29(1.21-1.38)	**<0.0001**	1.21(1.12-1.31)	**<0.0001**	1.51(1.31-1.72)	**<0.0001**
NYHA (I as reference)						
II	1.12(0.80-1.56)	0.48	1.11(0.77-1.61)	0.55		
III/IV	2.16(1.41-3.32)	**0.0004**	2.17(1.32-3.58)	**0.002**		
LVESDi, mm/m^2	1.05(1.03-1.08)	**<0.0001**	1.04(1.01-1.07)	**0.003**	1.03(0.98-1.08)	0.17
Model 3: LVESVi						
Age	1.06(1.05-1.08)	**<0.0001**	1.07(1.05-1.08)	**<0.0001**	1.06(1.02-1.10)	**0.0001**
Female	1.27(0.94-1.73)	0.12	1.53(1.07-2.19)	**0.019**	1.59(0.81-3.13)	0.17
Charlson comorbidity index	1.29(1.21-1.38)	**<0.0001**	1.22(1.13-1.33)	**<0.0001**	1.48(1.29-1.69)	**<0.0001**
NYHA (I as reference)						
II	1.10(0.79-1.54)	0.55	1.05(0.72-1.54)	0.77		
III/IV	2.05(1.33-3.18)	**0.001**	2.12(1.27-3.52)	**0.003**		
LVESVi per 10mm/m^2	1.05(0.99-1.10)	0.06	1.11(1.04-1.19)	**0.002**	1.10(1.00-1.20)	0.05

CI, confidence interval; HR, hazard ratio. See Table 1 for abbreviations.

*All-cause death occurred in 163 Taiwanese and 38 Japanese, respectively.

†After adjustment for age, sex, Charlson score, and NYHA, the HR per 1mm, CI, and P value of LVESD in the entire- , Taiwan- , Japan-cohort was 1.00(0.98-1.02), P=0.45 ; 1.02(1.00-1.04), P=0.035; and 1.01(0.97-1.05), P=0.39, respectively.

Figure 1. Adjusted cutoffs for risk of all-cause death in Taiwanese and Japanese.

Age-and sex-adjusted cutoffs in Taiwanese for left ventricular ejection fraction, left ventricular end-systolic dimension index and left ventricular end-systolic volume index (LVESVi) were 56%, 22mm/m^2, and 40ml/m^2, respectively. The corresponding cutoffs in Japanese were 55%, 24mm/m^2, and 48ml/m^2, respectively. Note that the spline curves for LVESVi were flat in the Japanese.

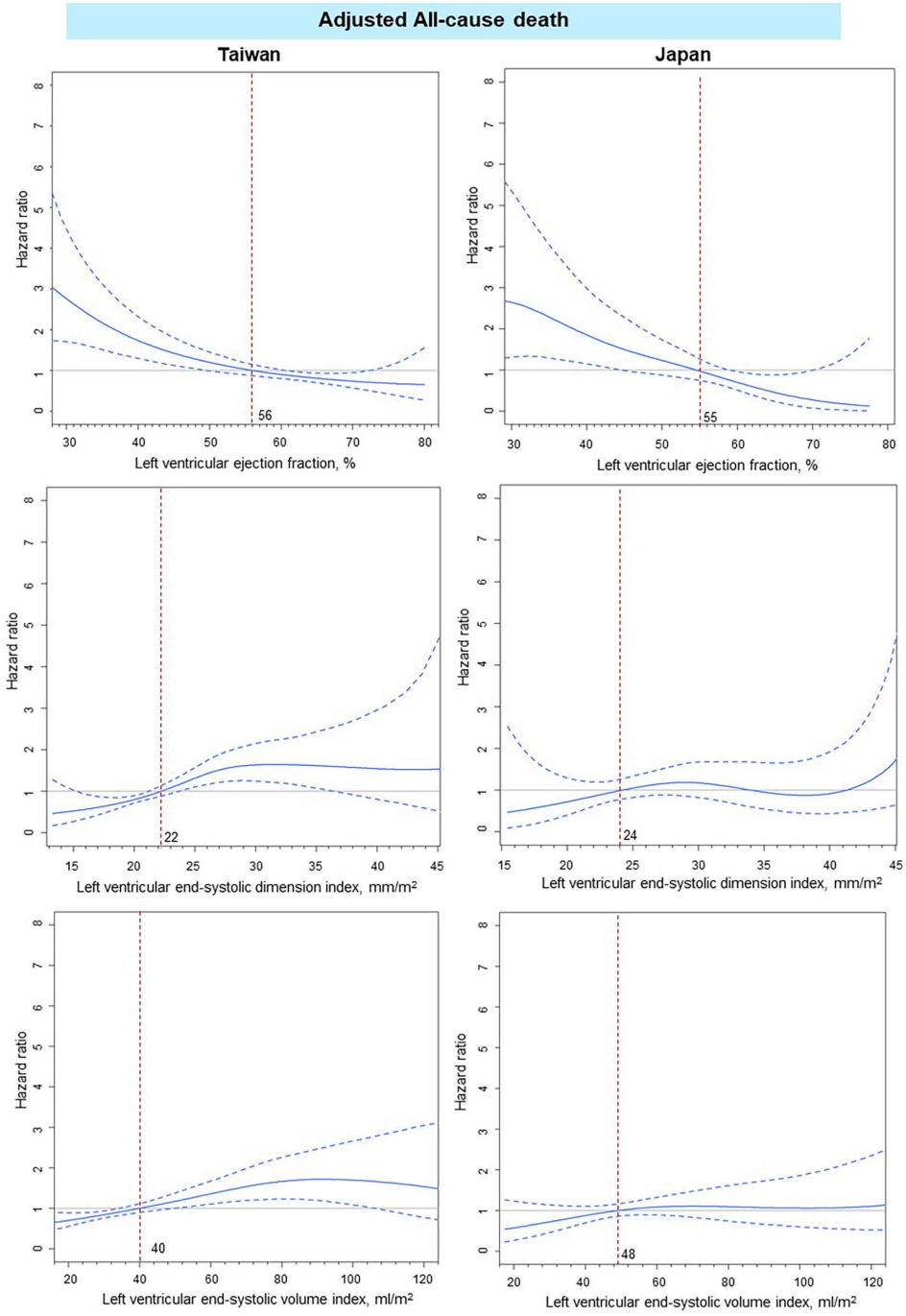

Figure 2. Adjusted cutoffs for risk of cardiovascular death in Taiwanese and Japanese. Age-and sex-adjusted cutoffs in the Taiwanese for left ventricular ejection fraction, left ventricular end-systolic dimension index and left ventricular end-systolic volume index (LVESVi) were 57%, 22mm/m^2, and 40ml/m^2, respectively. The corresponding cutoffs in Japanese were 50%, 25mm/m^2, and 52ml/m^2, respectively.