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Long-term outcomes in distinct phenogroups of patients with primary mitral regurgitation undergoing valve surgery

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ABSTRACT

Objectives Patients with mitral regurgitation (MR) may be heterogeneous with different risk profiles. We aimed to identify distinct phenogroups of patients with severe primary MR and investigate their long-term prognosis after mitral valve (MV) surgery.

Methods The retrospective cohort of patients with severe primary MR undergoing MV surgery (derivation, n=1629; validation, n=692) was analysed. Latent class analysis was used to classify patients into subgroups using 15 variables. The primary outcome was all-cause mortality after MV surgery.

Results During follow-up (median 6.0 years), 149 patients (9.1%) died in the derivation cohort. In the univariable Cox analysis, age, female, atrial fibrillation, left ventricular (LV) end-systolic dimension/volumes, LV ejection fraction, left atrial dimension and tricuspid regurgitation peak velocity were significant predictors of mortality following MV surgery. Five distinct phenogroups were identified, three younger groups (group 1–3) and two older groups (group 4–5): group 1, least comorbidities; group 2, men with LV enlargement; group 3, predominantly women with rheumatic MR; group 4, low-risk older patients; and group 5, high-risk older patients. Cumulative survival was the lowest in group 5, followed by groups 3 and 4 (5-year survival for groups 1–5: 98.5%, 96.0%, 91.7%, 95.6% and 83.4%; p<0.001). Phenogroups had similar predictive performance compared with the Mitral Regurgitation International Database score in patients with degenerative MR (3-year C-index, 0.763 vs 0.750, p=0.602). These findings were reproduced in the validation cohort.

Conclusion Five phenogroups of patients with severe primary MR with different risk profiles and outcomes were identified. This phenogrouping strategy may improve risk stratification when optimising the timing and type of interventions for severe MR.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Severe primary mitral regurgitation (MR) may be a heterogeneous disorder with different aetiology, clinical conditions and adverse cardiac remodelling. Even after the mitral valve (MV) surgery, the long-term prognosis is substantially different by the patients' comorbidities.

WHAT THIS STUDY ADDS

⇒ Using the data-driven latent class analysis, we demonstrated five distinct groups of patients with MR with different risk profiles. Each group was associated with different long-term mortality after MV surgery. Particularly, the phenogroups of predominantly women with rheumatic aetiology (group 3) and high-risk older patients (group 5) were associated with a high risk of mortality after the surgery. The phenogroup membership showed a similar predictive performance as the Mitral Regurgitation International Database risk score.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future studies are required to investigate whether a more tailored intervention strategy based on the phenotypes of severe MR improves patient outcomes.

INTRODUCTION

Severe primary mitral regurgitation (MR) is associated with significant mortality.[1] The decision for mitral valve (MV) surgery depends on the integrative assessment of MR aetiology, compensatory response of the left ventricle, symptoms and feasibility of MV repair.[2–4] Regarding the treatment strategies of MR, recent studies showed the potential benefits of early MV surgery for asymptomatic patients,[5 6] while a percutaneous edge-to-edge repair is now available for high-risk cases.[7 8] Long-term survival after operation may also be substantially different with patients' underlying comorbidities.[9] Therefore, patients with severe MR may be a heterogeneous population with various risk factors,[10–12] and identifying distinct phenogroups among these patients may help clinicians in tailoring individualised strategies.[13–15]

Recent studies have adopted a data-driven approach to identify meaningful phenotypes among a heterogeneous disease entity. Latent class analysis (LCA) is a useful tool to segregate samples into

homogeneous subgroups, which may improve risk stratification and determine the likelihood of treatment response.[16–18]

We hypothesised that there may be distinct phenogroups of patients with severe primary MR undergoing MV surgery with different long-term outcomes. We aimed to identify phenogroups of patients with severe MR using LCA and to provide insights into the optimal treatment strategy for severe primary MR.

METHODS

Study population

This study was conducted at three tertiary hospitals in South Korea (Asan Medical Center, Seoul National University Hospital and Seoul National University Bundang Hospital). Patients from Asan Medical Center were used for the development of the LCA model (=derivation cohort). Patients from the other centres were used as the validation cohort to examine whether phenogroups and their association with long-term mortality are reproduced in the external population.

Patients with severe primary MR who underwent MV surgery (MV repair or replacement) between 2006 and 2020 were retrospectively collected. Exclusion criteria were age <18 years, prior MV surgery or intervention, combined mitral stenosis ≥moderate, combined other severe valvular heart disease, MR due to infective endocarditis and secondary MR. Details of the data collection and variable definitions are presented in online supplemental methods.

Echocardiography

Transthoracic echocardiography was performed shortly before the MV surgery (median 21 days). Details of the echocardiography measurement are described in the online supplemental methods.

MR severity was determined by both qualitative and quantitative methods following the guideline.[19] Severe MR was confirmed by a large systolic regurgitant jet on the colour Doppler image, with an effective regurgitant orifice area of ≥0.40 cm^2 and a regurgitant volume of ≥60 mL by proximal isovelocity surface area methods. Degenerative MR includes MR due to flail leaflet or MV prolapse. Rheumatic MR was defined as diffuse MV leaflet thickening with restricted motion and rheumatic changes of MV observed in the surgical field. Congenital causes of MR included either cleft or parachute MV. MV morphology was evaluated in the patients with degenerative MR and categorised as either isolated anterior/posterior leaflet prolapse or bileaflet prolapse.

Outcome assessment

The primary endpoint was all-cause mortality after the MV surgery. Mortality data were ascertained by the official national death records provided by Statistics Korea for all participants. The time interval between the date of MV surgery to the last clinical follow-up or death was used as the follow-up duration.

Latent class analysis

LCA is an exploratory modelling technique of clustering subjects into homogeneous but mutually exclusive subgroups.[20] Using maximum likelihood estimation, LCA generates a robust class solution accounting for measurement errors and models' statistical fit.[21]

Fifteen variables were included for the LCA (online supplemental table 1). The criteria for the variable inclusion were (1) risk factors from the Society of Thoracic Surgeons score,[22] Mitral Regurgitation International Database (MIDA) score[23] or guidelines[2 3] and (2) statistical significance in the univariable Cox analysis (online supplemental table 2). The missing values were minimal and these were imputed with the *missForest* algorithm (online supplemental figure 1, methods).

LCA uses categorical variables as input. Thus, variables were categorised by the clinical consensus or cut-off values for surgical intervention (ie, left ventricular (LV) ejection fraction <60%) (online supplemental table 1). Mortality data were blinded in the LCA. LCA models were derived with the number of phenogroups ranging from 2 to 8. Multiple information criteria were calculated for each model,[21] and the optimal number of groups was determined based on the lowest value of these statistics. The minimal proportion of each group was set as 10% to prevent overfitting and ensure clinical interpretability.[16] Based on these criteria, the optimal number of groups was 5 (online supplemental figure 2).

Internal validation, sensitivity analysis and subgroup analysis

We performed an internal validation analysis to test the robustness of the group membership. Briefly, multinomial logistic regression models predicting phenogroups were developed and tested using the bootstrap samples (online supplemental methods). Additionally, a sensitivity analysis including both derivation and validation cohorts and a subgroup analysis of patients with degenerative MR were performed to test the reproducibility.[20]

External validation

Patients in the validation cohort (n=692) were allocated to one of the five groups based on the group probabilities derived from the LCA model (online supplemental methods).[16] The association between the phenogroups and outcomes was investigated as in the derivation cohort.

Statistical analysis

Continuous variables are presented as median (IQR) and categorical variables as frequencies (percentages). The difference between groups was compared using the analysis of variance test or Kruskal-Wallis test for continuous variables and the χ^2-test for categorical variables. Kaplan-Meier curves were plotted by groups and compared using the log-rank test. Cox proportional hazard analyses were used to evaluate the association between the phenogroups and mortality risk, and expressed as HRs with 95% CIs. Cox assumption was tested using Schoenfeld residuals.

The predictive performance of the phenogroup was compared with the MIDA score[23] in patients with degenerative MR. We calculated the MIDA score without pulmonary artery systolic pressure (ranged 0–10) due to the lack of data (online supplemental table 3). Harrell's C-index for 3-year mortality was calculated and compared using DeLong's method.

A two-tailed p value of <0.05 was considered statistically significant. All analyses were performed using R. The LCA was performed using the validated R package *poLCA*.[21]

Patient and public involvement

Patients or the public were not involved in the design, execution or dissemination plans of our research.

RESULTS

Cohort characteristics

In the derivation cohort, the majority of patients had degenerative MR (n=1375, 84.4%) and underwent MV repair (n=1349, 82.8%) (online supplemental table 4). MV repair was most

frequently performed in patients with degenerative MR (92.1%), while patients with rheumatic MR more frequently received MV replacement (57.2%) (p<0.001) (online supplemental figure 3). There was a tendency towards worse survival in patients with rheumatic MR, although statistically insignificant (p=0.145).

During a median 6.0 years follow-up (IQR 2.8–10.4 years), 149 patients (9.1%) died in the derivation cohort (online supplemental figure 4). In the univariable Cox analysis, age, female gender, atrial fibrillation (AF), LV end-systolic dimension/volumes, LV ejection fraction, LA dimension and tricuspid regurgitation (TR) peak velocity were significant predictors of mortality following MV surgery (online supplemental table 2).

Clinical characteristics of phenogroups by LCA

The LCA identified five distinct phenogroups in the derivation cohort (figure 1). Groups 1, 2 and 3 consisted of younger patients (median 44, 52 and 50 years), and groups 4 and 5 consisted of older patients (median 64 and 69 years) (table 1). Patients in group 1 were the youngest, least symptomatic and had the least comorbidities, such as AF (9.3%), across the five groups. Patients in group 2 were exclusively men (100%) with prevalent AF (65.5%). Among the groups with younger patients (groups 1–3), patients in group 2 had the highest prevalence of hypertension and diabetes (both p<0.001), and coronary artery bypass grafting was most frequently performed compared with group 1 or 3 (6.0% vs <1%, p<0.001). In contrast, patients in group 3 were predominantly women (78.9%) and frequently had AF. The most notable features of group 3 were the highest prevalence of rheumatic MR (67.3%) and the most frequent performance of MV replacement with mechanical valve (63.7%).

For the older groups (groups 4–5), patients in group 5 were older and had a higher proportion of AF compared with those in group 4 (71.4% vs 29.3%, p<0.001) (table 1). Patients in group 5 had the most frequent comorbidities and the lowest haemoglobin and glomerular filtration rate across the five groups.

Regarding the valve morphology in patients with degenerative MR, the isolated posterior leaflet prolapse was the most common in group 4 (68.4%, p<0.001), while isolated anterior leaflet and bileaflet prolapse was more common in group 3 and 5, respectively (table 1).

Cardiac remodelling characteristics of phenogroups

Echocardiography parameters were most favourable in group 1, with the small LV and LA dimensions, preserved LV ejection fraction and the lowest TR peak velocity across the five groups (table 2). Patients in group 2 had the largest LV dimensions and volumes across the five groups (LV end-systolic diameter 43 mm (40–47 mm), p<0.001), with the largest LA dimension (59 mm (55–65 mm), p<0.001) (table 2).

Patients in group 5 showed more advanced cardiac dysfunction compared with group 4, including increased LV dimensions, reduced LV ejection fraction and enlarged LA (all p<0.001) (table 2). The TR peak velocity was the highest in group 5 compared with the other four groups (3.3 m/s (3.0–3.6 m/s), p<0.001).

Clinical outcomes after MV surgery according to phenogroups

Cumulative survival was the lowest in group 5, followed by group 3 and then group 4 (5-year survival rate 83.4%, 91.7% and 95.6% for group 5, 3 and 4; p<0.001) (figure 2A). In the younger population (groups 1–3), group 3 had the worst cumulative survival, while mortality rarely occurred in group 1 (5-year survival rate 98.5%) (p<0.001) (figure 2B). In the groups with older patients (groups 4 and 5), group 5 demonstrated a markedly worse cumulative survival compared with group 4 (p<0.001) (figure 2C).

In the univariable Cox analysis with group 1 as the reference, there was a stepwise increased risk of mortality in the order of groups 2, 3 and 4, and 5 (table 3). After adjusting for covariates, the higher mortality risk associated with groups 3 and 5 remained significant (group 3, adjusted HR 2.61, 95% CI 1.08 to 6.32, p=0.034; group 5, adjusted HR 3.16, 95% CI 1.23 to 8.15, p=0.017).

Internal validation, sensitivity analysis and subgroup analysis

Internal validation analysis showed that multinomial logistic regression models had an average accuracy of 0.966 for the discrimination of phenogroups (online supplemental figure 5). The averaged F1 score and area under the receiver operating characteristic curves for each group were all >0.90 and >0.99, suggesting the robustness of the phenogroup assignment.

A sensitivity analysis including both derivation and validation cohorts similarly reproduced the five phenogroups and their association with mortality (ie, high-risk older patients conferring the worst survival) (online supplemental table 5, figure 6). In the subgroup analysis of degenerative MR, the optimal number of groups was 4. Each phenogroup in this subgroup analysis corresponded to the groups from the original LCA, except there was no group of women with rheumatic MR (group 3 in the original LCA). The mortality pattern of these four groups was again similar to the original LCA (online supplemental table 6, figure 7).

External validation

Patients in the validation cohort were older (median 61 vs 56 years, p<0.001) and had more comorbidities with more advanced cardiac dysfunction (online supplemental table 4). These patients were allocated to one of the five phenogroups according to the highest group probabilities (online supplemental table 7, methods). Distinct phenogroups in the derivation cohort were reproduced in the validation cohort with similar clinical and echocardiographic characteristics (online supplemental table 8).

During a median 5.2 years (IQR 2.8–7.9 years), 85 patients (12.3%) died in the validation cohort, which was significantly higher than the derivation cohort (p<0.001) (online supplemental figure 4). Similarly, the cumulative survival was the lowest in group 5, followed by groups 3 and 4 (5-year survival rate 78.5%, 93.5% and 91.0% for group 5, 3 and 4; p<0.001) (figure 2).

In the combined population of the derivation and validation cohorts (n=2321), group 3 and 5 were again associated with a higher mortality risk compared with group 1 in the multivariable Cox analysis (group 3, adjusted HR 3.24, 95% CI 1.45 to 7.25, p=0.004; group 5, adjusted HR 3.55, 95% CI 1.53 to 8.24, p=0.003) (table 3).

Risk stratification using the phenogroup information

In patients with degenerative MR across the entire cohort (n=1979), there was a stepwise increase in cumulative mortality of 1, 3 and 5 years with higher MIDA score without pulmonary artery systolic pressure (p<0.001) (online supplemental figure 8). In the entire cohort, the MIDA score demonstrated fair predictability for 3-year mortality (C-index 0.750, 95% CI 0.704 to 0.796), and the

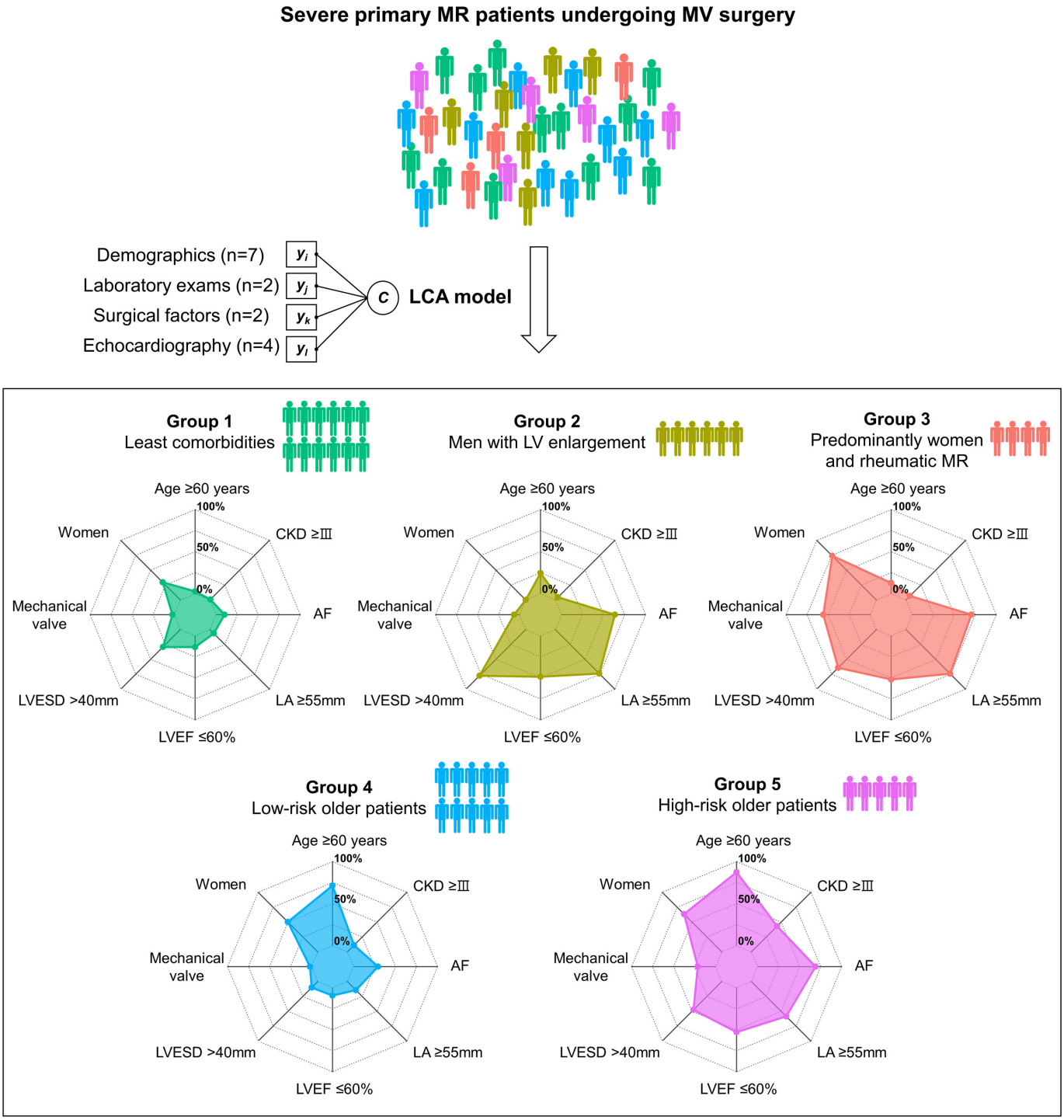

Figure 1 Data-driven phenogrouping of patients with severe primary MR undergoing MV surgery. Patients with severe primary MR undergoing MV surgery from three tertiary university hospitals were analysed (n=2321; derivation cohort, n=1629 and validation cohort, n=692). The latent variable (c) is estimated based on the 15 observed variables (y) of demographics, laboratory, surgical and echocardiographic factors by the expectation–maximisation algorithm, whose nominal categories are defined as latent classes (=groups). Five distinct groups were identified by LCA from the derivation cohort: group 1, least comorbidities (n=517); group 2, men with LV enlargement (n=249); group 3, predominantly women and rheumatic MR (n=171); group 4, low-risk older patients (n=461); and group 5, high-risk older patients (n=231). The prevalence of eight major risk factors in each phenogroup is depicted as a radar plot. The lines of the innermost octagon indicate zero prevalence. The phenogrouping may be used to guide clinicians to improve risk stratification and to provide a more tailored treatment strategy, as a step towards precision medicine in valvular heart disease. AF, atrial fibrillation; CKD, chronic kidney disease; LA, left atrium; LCA, latent class analysis; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement.

phenogroup information showed similar predictive performance (C-index 0.763, 95% CI 0.718 to 0.809) (p=0.602 for comparison) (online supplemental figure 8). In the validation cohort, the phenogroup and MIDA score again showed similar predictability (C-index 0.732 vs 0.731, p=0.960 for comparison).

Table 1 Baseline characteristics of the study participants according to phenogroups by LCA in the derivation cohort

	Younger population			Older population		
	Group 1	Group 2	Group 3	Group 4	Group 5	
	(n=517)	(n=249)	(n=171)	(n=461)	(n=231)	
Charcteristics	Least comorbidities	Men with LV enlargement	Predominantly women rheumatic MR	Low-risk order patients	High-risk older patients	P*
Age (year)	44 (37–51)	52 (46–59)	50 (39–56)	64 (59–69)	69 (64–74)	<0.001
Men, n (%)	365 (70.6)	249 (100.0)	36 (21.1)	230 (49.9)	78 (33.8)	<0.001
Body mass index (kg/m²)	24.1 (21.9–26.2)	25.3 (23.2–27.6)	22.9 (20.7–24.7)	25.0 (22.8–27.2)	22.7 (20.9–24.8)	<0.001
Comorbidities, n (%)						
Hypertension	100 (19.3)	91 (36.5)	2 (1.2)	291 (63.1)	117 (50.6)	<0.001
Diabetes	5 (1.0)	15 (6.0)	2 (1.2)	65 (14.1)	46 (19.9)	<0.001
A F	48 (9.3)	163 (65.5)	126 (73.7)	135 (29.3)	165 (71.4)	<0.001
Stroke	3 (0.6)	11 (4.4)	3 (1.8)	6 (1.3)	9 (3.9)	0.001
Myocardial infarction	5 (1.0)	7 (2.8)	1 (0.6)	5 (1.1)	12 (5.2)	<0.001
Year of MV surgery						<0.001
2006–2013	253 (48.9)	118 (47.4)	108 (63.2)	184 (39.9)	120 (51.9)	
2014–2020	264 (51.1)	131 (52.6)	63 (36.8)	277 (60.1)	111 (48.1)	
Symptomatic MR, n (%)	104 (20.1)	113 (45.4)	82 (48.0)	148 (32.1)	101 (43.7)	<0.001
Symptoms, n (%)						
Dyspnoea	83 (16.1)	94 (37.8)	69 (40.4)	129 (28.0)	93 (40.3)	<0.001
Chest pain	21 (4.1)	14 (5.6)	6 (3.5)	15 (3.3)	5 (2.2)	0.341
Oedema	5 (1.0)	6 (2.4)	9 (5.3)	5 (1.1)	11 (4.8)	<0.001
Palpitation	12 (2.3)	19 (7.6)	17 (9.9)	21 (4.6)	10 (4.3)	<0.001
Syncope	6 (1.2)	0 (0.0)	2 (1.2)	5 (1.1)	3 (1.3)	0.560
Laboratory results						
Haemoglobin (g/L)	140 (129–148)	145 (139–154)	127 (119–137)	130 (120–141)	120 (108–131)	<0.001
eGFR (mL/min/1.73 m2)	101.5 (92.8–110.3)	85.5 (76.0–97.1)	95.1 (79.3–106.5)	83.3 (69.7–91.4)	62.4 (48.7–79.5)	<0.001
MR aetiology, n (%)						<0.001
Degenerative	490 (94.8)	231 (92.8)	51 (29.8)	445 (96.5)	158 (68.4)	
Rheumatic	21 (4.1)	14 (5.6)	115 (67.3)	15 (3.3)	71 (30.7)	
Congenital	6 (1.2)	4 (1.6)	5 (2.9)	1 (0.2)	2 (0.9)	
Valve morphology in degenerative MR, n (%)†						<0.001
Isolated anterior leaflet prolapse	100 (20.4)	26 (11.3)	18 (35.3)	54 (12.2)	35 (22.6)	
Isolated posterior leaflet prolapse	267 (54.5)	138 (59.7)	20 (39.2)	303 (68.4)	72 (46.5)	
Bileaflet prolapse	123 (25.1)	67 (29.0)	13 (25.5)	86 (19.3)	48 (30.4)	
MR surgery type, n (%)						<0.001
MV repair	506 (97.9)	236 (94.8)	53 (31.0)	445 (96.5)	109 (47.2)	
MV replacement (mechanical)	11 (2.1)	13 (5.2)	109 (63.7)	8 (1.7)	51 (22.1)	
MV replacement (bioprosthetic)	0 (0.0)	0 (0.0)	9 (5.3)	8 (1.7)	71 (30.7)	
Concomitant CABG, n (%)	0 (0.0)	15 (6.0)	1 (0.6)	33 (7.2)	45 (19.5)	<0.001
Concomitant surgical atrial ablation, n (%)	44 (8.5)	150 (60.2)	100 (58.5)	123 (26.7)	138 (59.7)	<0.001

Values are expressed in median (IQR) or numbers (percentage).
*Comparison between five groups.
†MV morphology was assessed only in the subgroup of patients with degenerative MR (unavailable in five patients).
AF, atrial fibrillation; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LCA, latent class analysis; LV, left ventricular; MR, mitral regurgitation; MV, mitral valve.

DISCUSSION

Using the LCA, we demonstrated five distinct phenogroups of patients with severe primary MR undergoing MV surgery and their association with long-term mortality. Each group had distinct risk factor profiles in demographics, comorbidities, MR aetiology, surgery type and adverse cardiac remodelling (figure 1). Long-term mortality after MV surgery was markedly different by the phenogroups, and phenogroups

Table 2 Echocardiography parameters of the study participants according to phenogroups by LCA in the derivation cohort

	Younger population			Older population		
	Group 1 (n=517)	Group 2 (n=249)	Group 3 (n=171)	Group 4 (n=461)	Group 5 (n=231)	
	Least comorbidities	Men with LV enlargement	Predominantly women with rheumatic MR	Low-risk older patients	High-risk older patients	P value*
LV end-systolic diameter (mm)	37 (34–40)	43 (40–47)	41 (38–45)	34 (32–37)	39 (35–44)	<0.001
LV end-diastolic diameter (mm)	60 (56–63)	65 (61–69)	61 (56–65)	57 (54–60)	60 (56–65)	<0.001
LV end-systolic volume (mL)	57 (47–68)	78 (61–93)	61 (47–78)	46 (37–57)	55.5 (40–71)	<0.001
LV end-diastolic volume (mL)	164 (136–195)	193 (162–230)	147 (117–185)	139 (113–165)	135 (110–168)	<0.001
LV end-systolic volume index (mL/m^2)	31.7 (26.5–37.7)	41.6 (32.5–50.0)	37.8 (29.5–48.4)	26.6 (22.0–32.7)	34.6 (25.8–44.6)	<0.001
LV end-diastolic volume index (mL/m^2)	91.2 (76.2–109.6)	102.1 (86.0–122.6)	90.3 (73.5–111.9)	81.3 (67.0–97.5)	85.2 (70.4–107.5)	<0.001
LV ejection fraction (%)	65.0 (61.7–68.2)	60.2 (54.7–65.0)	58.9 (53.0–63.1)	66.4 (62.8–70.0)	59.8 (54.0–65.1)	<0.001
LV mass index (g/m^2)	124.3 (108.1–142.1)	151.6 (133.9–175.4)	129.4 (109.5–155.9)	127.4 (108.8–146.4)	145.6 (122.0–168.2)	<0.001
LA dimension (mm)	46.0 (42.0–50.0)	59.0 (55.0–65.0)	59.0 (55.5–64.5)	48.0 (44.0–52.0)	56.5 (51.0–63.0)	<0.001
E-wave (m/s)	1.14 (0.98–1.37)	1.44 (1.21–1.66)	1.60 (1.28–2.06)	1.22 (1.00–1.44)	1.40 (1.20–1.62)	<0.001
e′-wave (cm/s)	9.0 (7.4–10.6)	7.8 (6.2–9.1)	7.2 (6.0–9.0)	6.6 (5.6–7.9)	6.2 (5.0–7.8)	<0.001
E/e′ ratio	12.0 (10.0–15.0)	16.0 (13.0–22.0)	19.0 (14.0–33.0)	17.0 (13.0–21.0)	20.0 (15.0–29.0)	<0.001
TR peak velocity, m/s	2.5 (2.3–2.8)	3.1 (2.7–3.4)	2.9 (2.6–3.3)	2.8 (2.5–3.3)	3.3 (3.0–3.6)	<0.001

Values are expressed in median (IQR).
*Comparison between five groups.
AF, atrial fibrillation; LA, left atrium; LCA, latent class analysis; LV, left ventricular; MR, mitral regurgitation; TR, tricuspid regurgitation.

provided important predictive information for postsurgical mortality. This study demonstrates how phenomapping by data-driven analysis improves risk stratification and may guide clinicians when optimising the outcome of valvular heart disease patients.

Deciding the optimal timing of intervention for severe primary MR is challenging. The goal of MR treatment is to correct the diseased valve before LV dysfunction develops.[2 3] Although the guidelines define the one-size-fits-all cut-off values for the intervention (ie, LV end-systolic diameter >40 mm),[2 3] this may lead to significant misclassification, given the substantial heterogeneity of severe MR. A better characterisation of patients with severe MR may be required for more tailored therapy.[10]

Among the younger groups (groups 1–3), group 2 consisted of exclusively men (100%) with degenerative MR, whereas group 3 was predominantly women (78.9%) with rheumatic MR (table 1), suggesting significant sex-related differences in MR aetiology. Studies have shown that women have a higher prevalence of rheumatic MR than men,[24 25] which often requires MV replacement than MV repair.[4 26] Importantly, MV replacement is more frequently associated with valve-related complications, including thromboembolism or bleeding and reoperation.[26 27] Consistent with the literature, patients in group 3 (*predominantly women and rheumatic MR*) most frequently underwent MV replacement with mechanical valve (63.7%) and had the second-worst survival across the five groups despite young age (figure 2). In contrast, young men with enlarged left ventricles (group 2) showed a favourable prognosis comparable to those with the least comorbidities (group 1). These highlight significant sex differences in severe MR and suggest close monitoring of adverse events may be required for women with rheumatic MR.

Among the older patients, group 4 (*low-risk older patients*) had fewer comorbidities and less cardiac dysfunction than group 5 (*high-risk older patients*). Notably, patients in group 4 showed excellent long-term survival after surgery (5-year cumulative survival, 95.6%) (figure 2). In the contemporary era, the expected survival after MV repair may be equivalent to that of the age-matched general population,[28] and the feasibility of MV repair is an important factor in determining the timing of intervention.[2 3] The patients with degenerative MR in group 4 had the most prevalent posterior leaflet prolapse, for which MV repair is performed with a higher success rate and longer durability compared with other complex MV morphology (ie, anterior leaflet prolapse).[4 29] Given the lower operative risk of group 4, earlier MV repair may be reasonable if successful repair is highly expected.[2 3] However, for group 5, the prognosis was dismal, with more than a 10% mortality within the 1-year postsurgical period (figure 2). Therefore, whether the benefit of MV surgery outweighs the risk should be carefully evaluated in patients of group 5, and percutaneous edge-to-edge repair may be a more appropriate strategy if feasible.[7 8]

Our phenogrouping also provides important information on the outcomes of asymptomatic patients with severe MR. Although debatable, recent studies suggest that early MV surgery may be superior to watchful waiting in asymptomatic patients with severe MR.[5 6] Our study also demonstrated nearly perfect long-term survival of group 1 patients after MV surgery (figure 2), the majority of which were asymptomatic. A randomised trial is currently ongoing to test this hypothesis (NCT03389542), and our phenogroups here may provide important insights when selecting the candidates for early surgery.

The most optimal timing and type of intervention may be different by phenogroups, which could be explored in future hypothesis-driven studies. Importantly, the group membership can be assigned to any other population using our model (online supplemental methods).[16] Our external validation analysis showed that the phenogroups and their associations with mortality were reproduced in populations from different hospitals, indicating generalisability. The phenogroup membership alone had similar predictability with the MIDA score. Therefore, the phenogroup information has major potential to improve risk stratification and may offer a novel target for specific treatment strategies. For the step toward precision medicine, we are currently constructing a large database incorporating patients with valvular heart disease across key institutions in South Korea to establish and validate the data-driven risk stratification.

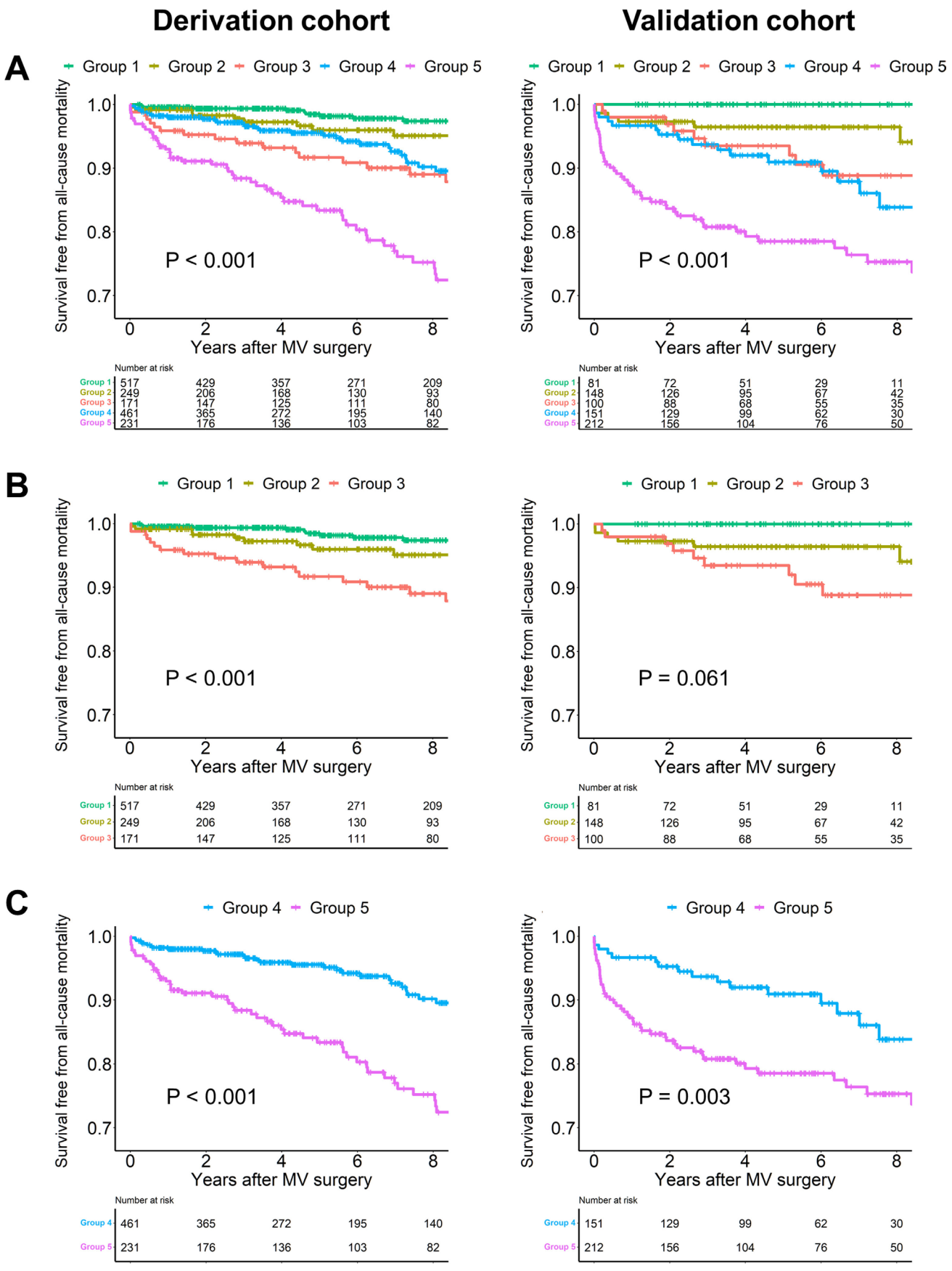

Figure 2 Cumulative survival after MV surgery according to phenogroups by LCA. Kaplan-Meier survival curves of all-cause mortality by the phenogroups in the derivation cohort (left panel) and the validation cohort (right panel). Kaplan-Meier curves were plotted for the (A) entire patients (groups 1–5) and further stratified by (B) younger patients (groups 1–3) and (C) older patients (groups 4–5). LCA, latent class analysis; MV, mitral valve.

Table 3 Association of phenogroups with mortality risk after MV surgery

	Derivation cohort (n=1629)		Entire cohort (n=2321)	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariable analysis				
Group 1	1.00 (reference)	–	1.00 (reference)	–
Group 2	2.78 (1.22 to 6.35)	0.015	3.48 (1.65 to 7.36)	0.001
Group 3	5.93 (2.81 to 12.52)	<0.001	6.40 (3.14 to 13.05)	<0.001
Group 4	5.34 (2.67 to 10.68)	<0.001	6.45 (3.30 to 12.64)	<0.001
Group 5	16.78 (8.61 to 32.69)	<0.001	18.78 (9.84 to 35.86)	<0.001
Multivariable analysis**				
Group 1	1.00 (reference)	–	1.00 (reference)	–
Group 2	1.04 (0.39 to 2.77)	0.944	1.45 (0.62 to 3.43)	0.392
Group 3	2.61 (1.08 to 6.32)	0.034	3.24 (1.45 to 7.25)	0.004
Group 4	1.85 (0.81 to 4.20)	0.144	2.08 (0.97 to 4.46)	0.058
Group 5	3.16 (1.23 to 8.15)	0.017	3.55 (1.53 to 8.24)	0.003

*Adjusted for variables included in the MIDA score (age, atrial fibrillation, symptoms, LV end-systolic diameter, LV ejection fraction, LA dimension and TR peak velocity).
LA, left atrium; LV, left ventricular; MIDA, Mitral Regurgitation International Database; MV, mitral valve; TR, tricuspid regurgitation.

Limitations

First, the LCA model was derived from a single centre (n=1629). However, sensitivity and subgroup analyses demonstrated that similar phenogroups were reproduced in different populations, indicating robustness.[20] Second, this cohort included patients across 14 years. Given that indications and surgical techniques have changed over the period, this may have influenced our findings. Third, pulmonary artery systolic pressure data were unavailable. However, recent guidelines suggest using TR peak velocity alone to assess pulmonary hypertension since the right atrial pressure estimation based on inferior vena cava may be error-prone.[30] Lastly, as we exclusively enrolled patients with MR undergoing MV surgery, phenogroups of patients not undergoing imminent intervention may be different.

CONCLUSION

Five phenogroups of patients with severe primary MR with different long-term prognosis after MV surgery were identified. This phenogrouping strategy may be used to improve risk stratification and, potentially, to individualise patient management when optimising the timing and types of interventions for severe primary MR.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants, and the institutional review board of each study centre approved the protocol (Asan Medical Center: S2020-3037-0002, Seoul National University Hospital: 1810-030-977 and Seoul National University Bundang Hospital: B-1811-507-402). Written informed consent was waived due to the use of anonymised information and the retrospective nature of the study design.

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