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Original Article
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Shifts in Clinical Characteristics, Treatment, and Outcome for Rheumatic Mitral Stenosis: Insights From a 20-Year Multicentre Registry Study in Korea

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ABSTRACT

Background: The rapid economic development of South Korea provides a unique model to study changes in the clinical characteristics, treatment approaches, and clinical outcomes of patients with rheumatic mitral stenosis (MS) relative to socioeconomic growth.
Methods: From the Multicenter mitrAl STEnosis with Rheumatic etiology (MASTER) registry, 2,337 patients diagnosed with moderate or severe rheumatic MS between January 2001 and December 2020 were analyzed. Patients were grouped into consecutive 5-year intervals based on their year of diagnosis. Clinical characteristics, echocardiographic data, and clinical outcomes were assessed.
Results: Over 20 years, the severity of mitral stenosis increased from 79.1% to 90.2%; similarly, the average age at diagnosis increased from 54.3 to 63.0 years (all $P < 0.001$). Comorbidities such as hypertension and atrial fibrillation increased (6.3% to 29.5% and 41.4% to 46.9%, respectively; all P for trend < 0.05). The rate of mitral intervention within five years after diagnosis increased from 31.2% to 47.4% (P for trend < 0.001). However, clinical outcomes of rheumatic mitral stenosis deteriorated over time in the composite outcomes (log-rank test, $P < 0.001$). Conversely, the incidence of stroke remained stable (60.6–73.7%; $P < 0.001$), which might be attributed to the increased use of anticoagulation therapy.
Conclusion: This study observed an increase in patient age, comorbidities, and valve disease severity as the country transitioned from a developing to developed status. Despite a rise in mitral valve interventions, clinical outcomes deteriorated over 20 years, highlighting the need for modified treatment approaches to improve patient outcomes.

Keywords: Trend Change; Rheumatic Mitral Stenosis; Rheumatic Heart Disease; Korea

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Disclosure

The authors have no potential conflicts of interest to disclose.

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INTRODUCTION

Rheumatic heart disease (RHD), especially mitral stenosis (MS), is a complication arising from acute rheumatic fever, and it contributes to cardiovascular death and disability, predominantly in low- and middle-income countries.[1-3] Advancements in living conditions, nutrition, access to medical treatment, and penicillin use have significantly reduced the incidence of acute rheumatic fever, leading to a decline in RHD prevalence among adults.[4] However, there remains a paucity of information regarding changes in patient characteristics, concomitant valve disease, treatment approaches, and clinical outcomes in patients with MS relative to socioeconomic development.

In this regard, the transition of South Korea from a developing country to a developed one within a half-century, offers a unique model for investigating changes in rheumatic MS.[5] In recent years, there has been a significant decrease in MS incidence in South Korea, with rates declining from 10.3% in 2007 to 3.6% in 2016[6]; the majority cases are primarily due to RHD.[7] Comprehensive data on patient characteristics, disease progression, and clinical outcomes based on evaluation and treatment remain limited. RHD has been significantly prevalent in regions with restricted medical access and was once common in developed countries before the development and adoption of advanced diagnostic and treatment modalities.[7] However, due to mandatory social health insurance and the extensive implementation of advanced imaging techniques such as echocardiography, accurate diagnosis and appropriate treatment of rheumatic MS have been achieved since the early phases of economic development.[8,9] Therefore, assessing the changes in patient characteristics, concomitant valve disease, treatment methods, and clinical outcomes of rheumatic MS during the socioeconomic evolution of South Korea may offer valuable insights into the natural history of MS through socioeconomic developments.

In this study, we investigated the shifts in clinical characteristics, treatment patterns, and clinical outcomes of patients with rheumatic MS over 20 years in South Korea.

METHODS

Study design and participants

The Multicenter mitrAl STEnosis with Rheumatic etiology (MASTER) registry is a multicentre, observational registry involving four tertiary hospitals in South Korea, with 3,140 participants diagnosed with moderate to severe rheumatic MS between January 2001 and December 2020. All study participants underwent transthoracic echocardiography at the time of initial diagnosis. Enrolled patients underwent an initial assessment, including collection of data regarding demographics, serial echocardiography, clinical events, and treatment for rheumatic MS, per standard practices at each participating institution. We excluded patients with prior mitral valve intervention (mitral valvuloplasty, percutaneous transvenous mitral commissurotomy, or open mitral commissurotomy [OMC]) or whose echocardiographic data could not be re-measured for analysis. Since this study was based on treatment-naive cases, cases that had received previous interventions were excluded.

A total of 2,337 patients met the study criteria and were grouped according to the year of diagnosis at intervals of consecutive 5-year periods (Period 1: before 2005, Period 2: 2006–2010, Period 3: 2011–2015, Period 4: after 2016) (**Fig. 1**). We analysed clinical characteristics

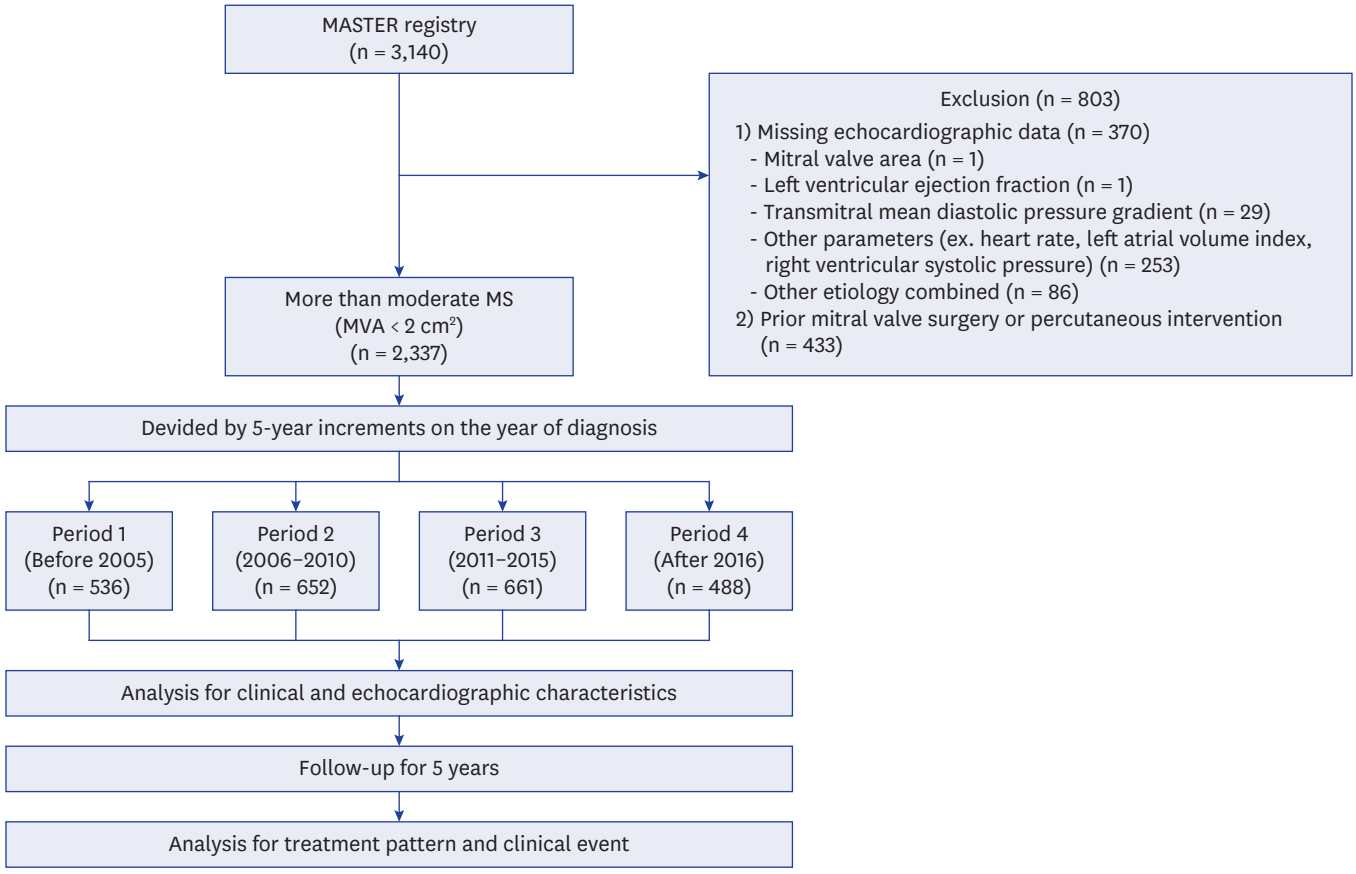

Fig. 1. Flowchart of the current study.
MASTER = Multicenter mitrAl STEnosis with Rheumatic etiology, MS = mitral stenosis, MVA = mitral valve area.

and echocardiographic data at initial diagnosis and investigated the changes in treatment patterns and clinical events prospectively for five years post-diagnosis.

Echocardiography

All patients underwent standard two-dimensional (2D) and Doppler evaluations using a conventional ultrasound machine, according to each centre's image acquisition protocol based on the American Society of Echocardiography guidelines.[10] The diagnostic criteria for rheumatic MS were based on World Heart Federation criteria for echocardiographic diagnosis of RHD.[11] Mitral valve area (MVA) was assessed using 2D planimetry at the leaflet tips at the mid-diastolic phase.[12,13] MVA by pressure half-time (PHT) calculation was performed using the following formula: 220/PHT. Using a continuous wave Doppler signal at both mitral valve leaflet tips, the mean diastolic pressure gradient (MDPG) was calculated. Right ventricular systolic pressure (RVSP) was determined by combining the peak systolic pressure from the maximal tricuspid regurgitation (TR) jet velocity with the right atrial pressure obtained by measuring the inferior vena cava diameter.

Definitions and endpoints

The baseline characteristics included age, sex, and comorbidities, including hypertension, diabetes, chronic kidney disease (CKD), atrial fibrillation (AF), stroke, and the prescriptions for anticoagulation therapies, such as vitamin K antagonist and non-vitamin K antagonist

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oral anticoagulant. The mitral intervention included a composite of mechanical or bioprosthetic mitral valve replacement (MVR), percutaneous mitral valvuloplasty (PMV), or OMC. Significant valvular dysfunction was defined as a more-than-moderate grade of valvular disease. A more-than-moderate grade of rheumatic MS was defined as MVA < 2.0 cm^2. Low gradient severe MS referred to patients with a transmitral MDPG < 5 mmHg among patients with an MVA < 1.5 cm^2.

Because of differences in the traceability of each period, we tried to investigate within the usually applicable timeframe of five years after diagnosis. Clinical outcomes were defined as individual events and the composite of all-cause mortality, heart failure (HF) hospitalisation, and ischaemic stroke within five years following the initial diagnosis. A dedicated physician or research nurse conducted follow-up for all-cause mortality and clinical events at each local institution. Death and clinical events were confirmed or determined by direct interview, telephone contact, or review of medical records. An adjudicating committee analysed clinical outcome data from each centre. The confirmation of death was double-checked via a query at the National Statistical Office.

Statistical analysis

We compared baseline characteristics, treatment strategy, and clinical outcomes (all-cause mortality, hospitalisation resulting from aggravating HF, and stroke) across the periods. Baseline characteristics are summarised as the mean ± standard deviation or median (interquartile range; IQR) for continuous variables and as frequency with percentages for categorical variables Continuous variables were compared using the *t*-test and categorical variables compared using either the χ^2 test or Fisher's exact test as appropriate. The Cochran–Armitage and Jonckheere–Terpstra methods were used to test trends in nominal and categorical variables across periods. Statistical significance was defined as $P < 0.05$. Kaplan–Meier survival analysis was performed to evaluate the association of all-cause death, HF hospitalisation, and stroke. All statistical analyses were performed using R statistical software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement

The Institutional Review Board of Severance Hospital approved this study (approval number: 4-2022-0214), which was conducted in compliance with the Declaration of Helsinki. The need for informed consent was waived.

RESULTS

Temporal trends in clinical characteristics of patients with rheumatic MS

The study enrolled 2,337 patients, of which 1,741 (74.5%) were women. The average age of the study population was 58.8 ± 12.6 years. **Table 1** summarises the baseline characteristics according to consecutive 5-year periods. Over 20 years, the average age of patients diagnosed with moderate or severe rheumatic MS significantly increased, from an average of 54.3 ± 11.6 years in Period 1 to 63.0 ± 12.1 years in Period 4 (*P* value for trend < 0.001; **Fig. 2A**). The proportion of females in the study remained stable, with a female predominance ranging from 74.8% to 77.0% (*P* for trend = 0.201). The number of patients with rheumatic MS who exhibited comorbidities, including hypertension, diabetes, CKD, AF, and previous stroke, gradually increased. Notably, severe grade rheumatic MS was frequently encountered at the first diagnosis, compared to that in the past (severe grade at first diagnosis: 79.1–90.2%, *P* for trend < 0.001).

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Table 1. Characteristics at initial diagnosis, stratified by year

Variables	Total (n = 2,337)	Period 1 (before 2005) (n = 536)	Period 2 (2006–2010) (n = 652)	Period 3 (2011–2015) (n = 661)	Period 4 (after 2016) (n = 488)	*P* value for trend
Clinical characteristics						
Age at diagnosis						< 0.001
Mean ± SD	58.8 ± 12.6	54.3 ± 11.6	57.8 ± 12.9	60.4 ± 12.0	63.0 ± 12.1	
Median [IQR]	59.0 [50.0–68.0]	55.0 [47.0–63.0]	59.0 [48.0–68.0]	61.0 [53.0–70.0]	63.0 [54.0–72.0]	
Sex						0.201
Male	595 (25.5)	135 (25.2)	187 (28.7)	161 (24.4)	112 (23.0)	
Female	1,742 (74.5)	401 (74.8)	465 (71.3)	500 (75.6)	376 (77.0)	
Comorbidity						
Hypertension	474 (20.3)	34 (6.3)	109 (16.7)	187 (28.3)	144 (29.5)	< 0.001
Diabetes	279 (11.9)	30 (5.6)	71 (10.9)	122 (18.5)	56 (11.5)	< 0.001
CKD	70 (3.0)	4 (0.7)	17 (2.6)	26 (3.9)	23 (4.7)	< 0.001
AF	960 (41.1)	222 (41.4)	238 (36.5)	271 (41.0)	229 (46.9)	0.029
Previous stroke	271 (11.6)	36 (6.7)	79 (12.1)	93 (14.1)	63 (12.9)	< 0.001
Use of anticoagulation	544 (23.3)	22 (4.1)	184 (27.3)	177 (26.0)	161 (32.3)	< 0.001
Symptomatic MS	1,576 (67.4)	345 (64.4)	446 (68.4)	451 (68.2)	334 (68.5)	0.180
Severe MS at diagnosis	1,955 (83.7)	424 (79.1)	528 (81.0)	563 (85.2)	440 (90.2)	< 0.001
Moderate MS at diagnosis	382 (16.3)	112 (20.9)	124 (19.0)	98 (14.8)	48 (9.8)	< 0.001[a]
Echocardiographic characteristics						
LVEF, %	60.9 ± 10.2	62.4 ± 8.9	60.6 ± 10.1	60.4 ± 10.1	60.2 ± 11.4	0.985
MDPG, mmHg	7.0 ± 3.9	6.8 ± 4.0	7.3 ± 4.3	7.2 ± 3.6	6.7 ± 3.6	0.086
MVA, cm^2	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	0.998
LAVI, mL/m^2	78.0 ± 48.8	67.0 ± 36.1	74.9 ± 41.6	82.6 ± 61.5	81.8 ± 42.6	0.054
RVSP, mmHg	38.1 ± 14.7	35.4 ± 13.1	39.3 ± 15.6	38.2 ± 14.6	39.1 ± 15.0	< 0.001
Significant[b] MR	1,270 (54.3)	271 (50.6)	335 (51.4)	371 (56.1)	293 (60.0)	0.001
Significant AS	612 (26.2)	89 (16.6)	170 (26.1)	197 (29.8)	156 (32.0)	< 0.001
Significant AR	1,066 (45.6)	207 (38.6)	295 (45.3)	320 (48.4)	244 (50.1)	< 0.001
Significant TR	1,366 (58.5)	277 (51.7)	379 (58.1)	393 (59.5)	317 (65.0)	< 0.001
Mitral valve intervention and anticoagulation use						
Age at the intervention						
Mean ± SD	57.6 (12.0)	51.4 (12.0)	53.8 (12.1)	57.9 (11.5)	59.8 (10.5)	< 0.001
Median [IQR]	58.0 [49.0–67.0]	57.0 [49.0–67.0]	56.0 [47.0–67.0]	60.0 [50.5–67.0]	60.0 [52.0–67.0]	0.002
Mitral intervention[c] during 5-year	974 (41.7)	167 (31.2)	274 (42.0)	301 (45.5)	232 (47.5)	< 0.001
MVR	736 (31.5)	102 (19.0)	213 (32.7)	234 (35.4)	187 (38.3)	< 0.001
PMV	262 (11.2)	69 (12.9)	67 (10.3)	75 (11.3)	51 (10.5)	0.285
OMC	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	-
Anticoagulation after diagnosis	1,551 (66.4)	325 (60.6)	426 (65.4)	440 (66.6)	360 (73.7)	< 0.001
Other surgical intervention						
AVR in 5-year	282 (12.1)	30 (5.6)	87 (13.3)	85 (12.9)	80 (16.4)	< 0.001
SAVR	280 (12.0)	30 (5.6)	86 (13.2)	84 (12.8)	80 (16.4)	< 0.001
TAVR	2 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	-
TV surgery in 5-year	165 (7.1)	16 (3.0)	51 (7.8)	52 (7.9)	46 (9.4)	< 0.001
TVR	8 (0.3)	1 (0.1)	5 (0.1)	2 (0.1)	0 (0.1)	-
TAP	157 (6.8)	15 (6.4)	46 (7.1)	50 (7.6)	46 (9.4)	< 0.001
MAZE operation in 5-year	375 (16.0)	51 (9.5)	78 (12.0)	128 (19.4)	118 (24.2)	< 0.001

Values are presented as mean ± SD, median [IQR] or number (%).
SD = standard deviation, IQR = interquartile range, CKD = chronic kidney disease, AF = atrial fibrillation, MS = mitral stenosis, LVEF = left ventricular ejection fraction, MDPG = transmitral mean diastolic pressure gradient, MVA = mitral valve area, LAVI = left atrial volume index, RVSP = right ventricular systolic pressure, MR = mitral regurgitation, AS = aortic stenosis, AR = aortic regurgitation, TR = tricuspid regurgitation, MVR = mitral valve replacement, PMV = percutaneous mitral valvuloplasty, OMC = open mitral commissurotomy, AVR = aortic valve replacement, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement, TV = tricuspid valve, TVR = tricuspid valve replacement, TAP = tricuspid annuloplasty.
[a]*P* value for decreasing trend.
[b]Significant valvular dysfunction was defined as more than moderate grade of valvular disease.
[c]Mitral intervention is a composite of MVR, PMV, or OMC.

Temporal trends in echocardiographic characteristics of patients with rheumatic MS

There were no significant intergroup differences in the echocardiographic parameters (**Table 1**), including left ventricular ejection fraction, left ventricular end-diastolic and systolic dimensions,

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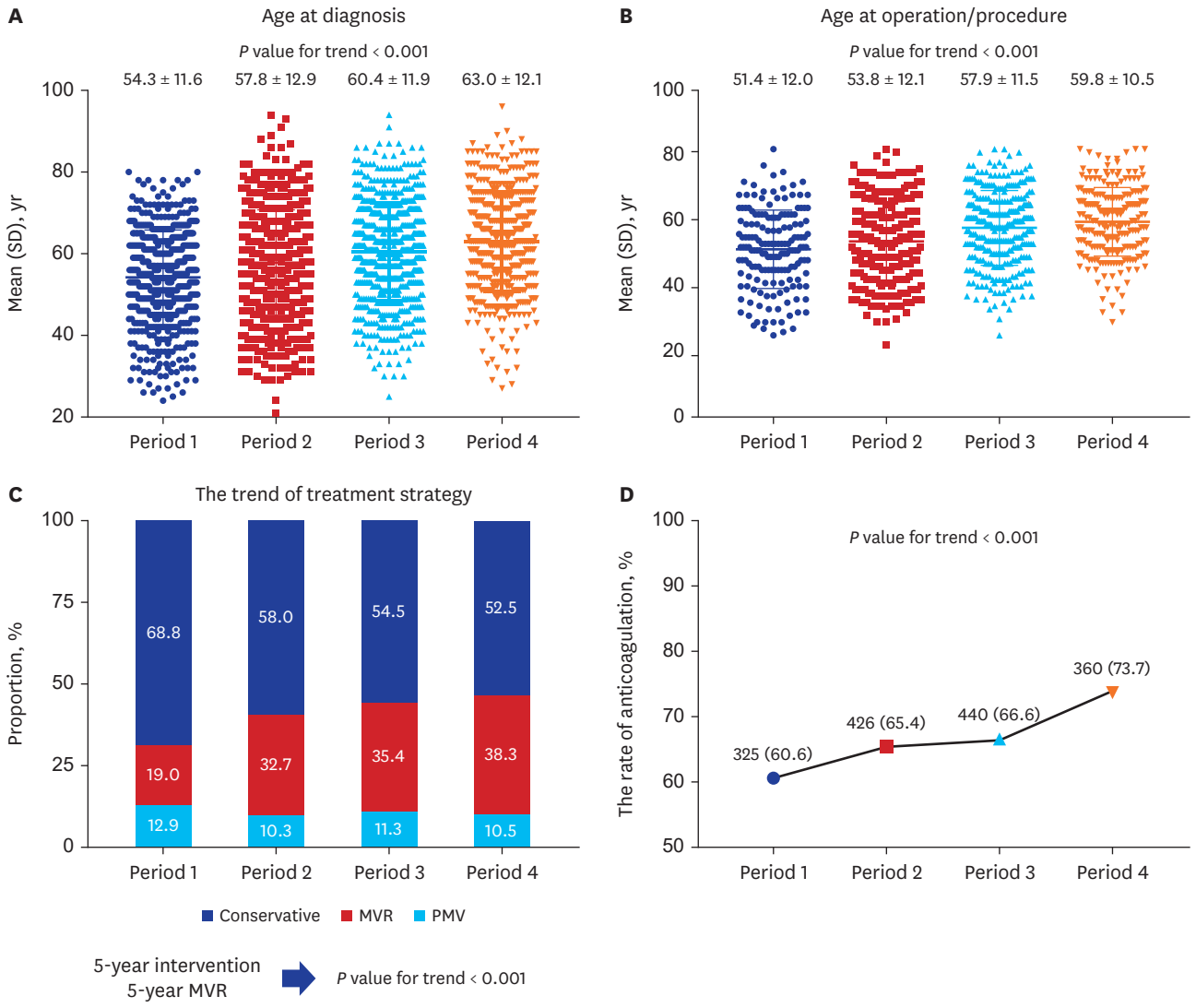

Fig. 2. Temporal trends of (**A**) ages at first diagnosis, (**B**) ages considering a mitral intervention, (**C**) type of treatment strategy, and (**D**) use of anticoagulation rate within five years after diagnosis.
Period 1: Before 2005, Period 2: 2006–2010, Period 3: 2011–2015, Period 4: After 2016 (Open commissurotomy was done in only one case in Period 1 and Period 3).
SD = standard deviation, MVR = mitral valve replacement, PMV = percutaneous mitral valvuloplasty.

MDPG, and MVA. However, RVSP significantly increased with time, from 35.4 ± 13.1 mmHg to 39.1 ± 15.0 mmHg (*P* for trend < 0.001) and left atrial volume index (LAVI) showed an increasing tendency from 67.0 ± 36.1 mL/m^2 to 81.8 ± 42.6 mL/m^2 (*P* for trend = 0.054). Additionally, the prevalence of concomitant valvular dysfunction, such as aortic stenosis (AS), aortic regurgitation (AR), and TR, steadily increased over time (all *P* for trend < 0.001).

Temporal trends of rheumatic MS treatment

As shown in **Table 1**, the average age at the mitral intervention increased over time, from 51.4 ± 12.0 years in Period 1 to 59.8 ± 10.5 years in Period 4 (*P* for trend < 0.001) (**Fig. 2B**). The proportion of patients receiving mitral intervention increased over time, with 47.5% of patients in Period 4 compared to 31.2% in Period 1 (*P* for trend < 0.001). Furthermore, the proportion of patients undergoing mitral intervention within five years of diagnosis increased from 31.2% in Period 1 to 47.5% in Period 4 (*P* for trend < 0.001). The rate of PMV remained similar over time

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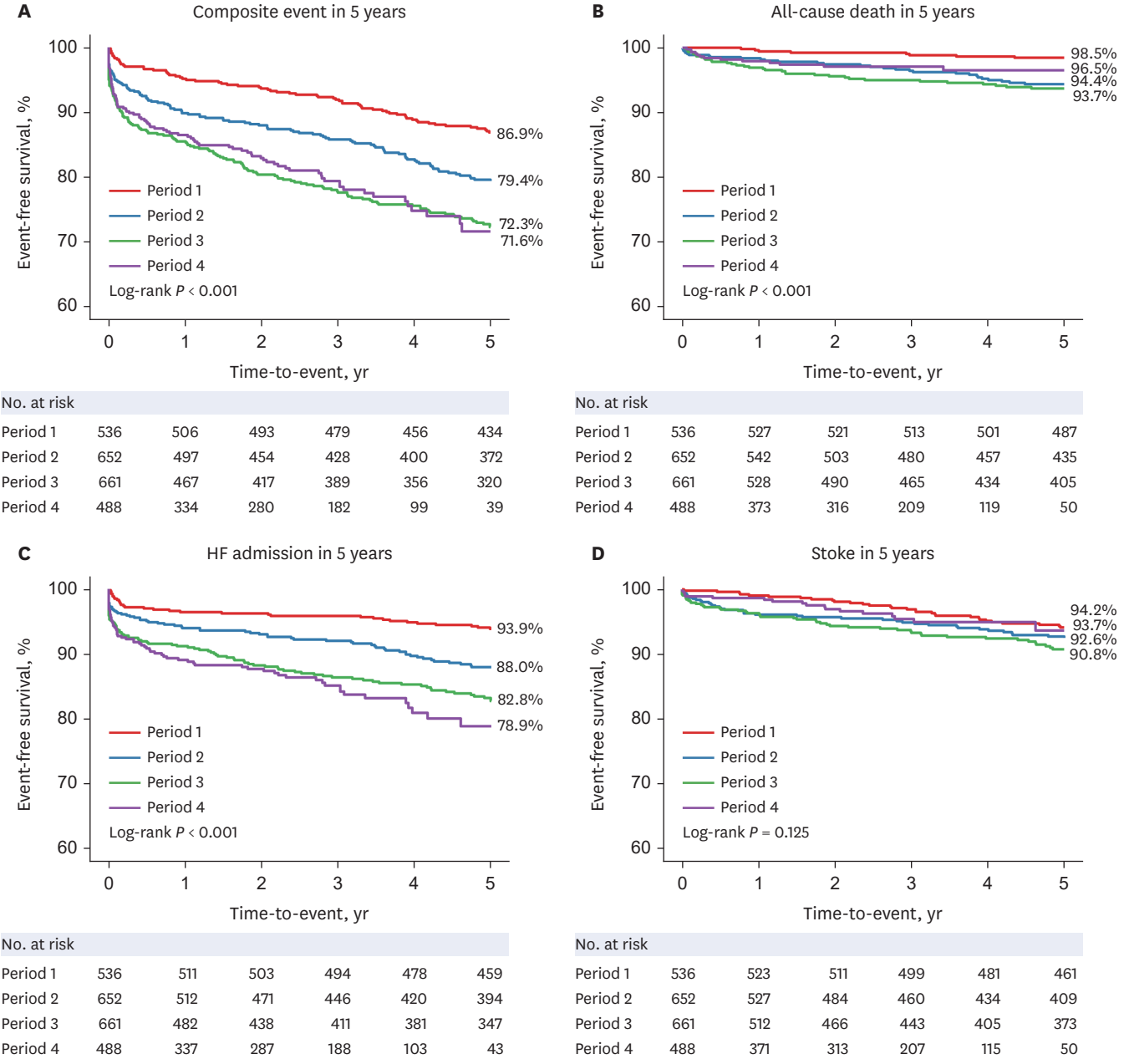
(*P* for trend = 0.285), while the rate of MVR showed an increasing trend (*P* for trend < 0.001). During the study period, OMC was rarely performed. Additionally, more patients commenced anticoagulant use within five years of diagnosis over the time of the study (*P* for trend < 0.001).

Temporal trends in prognosis in rheumatic MS treatment

During a median follow-up of 52.0 months (IQR: 33.5–70.5), composite outcome within five years after diagnosis deteriorated significantly from Period 1 to Period 4 (log rank test, *P* < 0.001; **Fig. 3A**). In addition, all-cause mortality increased, except for Period 4 (**Fig. 3B**);



No. at risk

Period 1	536	506	493	479	456	434
Period 2	652	497	454	428	400	372
Period 3	661	467	417	389	356	320
Period 4	488	334	280	182	99	39

No. at risk

Period 1	536	527	521	513	501	487
Period 2	652	542	503	480	457	435
Period 3	661	528	490	465	434	405
Period 4	488	373	316	209	119	50

No. at risk

Period 1	536	511	503	494	478	459
Period 2	652	512	471	446	420	394
Period 3	661	482	438	411	381	347
Period 4	488	337	287	188	103	43

No. at risk

Period 1	536	523	511	499	481	461
Period 2	652	527	484	460	434	409
Period 3	661	512	466	443	405	373
Period 4	488	371	313	207	115	50

Fig. 3. Temporal trends for cumulative incidences of composite outcome (**A**), all-cause death (**B**), hospitalization for HF (**C**), and ischemic stroke (**D**) were estimated using the Kaplan–Meier method.
Period 1: Before 2005, Period 2: 2006–2010, Period 3: 2011–2015, Period 4: After 2016.
HF = heart failure.

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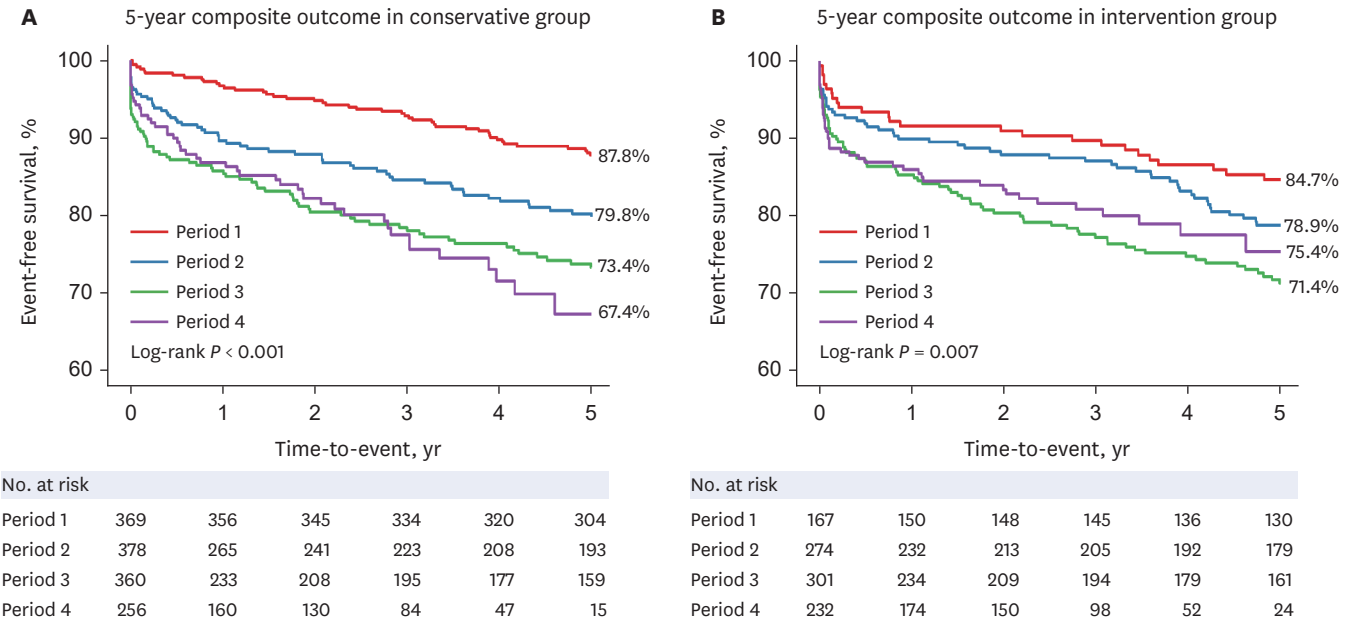

No. at risk						
Period 1	369	356	345	334	320	304
Period 2	378	265	241	223	208	193
Period 3	360	233	208	195	177	159
Period 4	256	160	130	84	47	15

No. at risk						
Period 1	167	150	148	145	136	130
Period 2	274	232	213	205	192	179
Period 3	301	234	209	194	179	161
Period 4	232	174	150	98	52	24

Fig. 4. The survival rate of composite outcome divided by period and treatment strategy.
Period 1: Before 2005, Period 2: 2006–2010, Period 3: 2011–2015, Period 4: After 2016.

the cumulative incidence of HF hospitalisation within five years steadily increased with time (log-rank test, $P < 0.001$; **Fig. 3C**). The incidence of stroke within five years showed a similar rate (log-rank test, $P = 0.453$; **Fig. 3D**). Regarding clinical outcomes based on treatment options, the prognosis of the group receiving conservative treatment consistently deteriorated (log-rank test, $P < 0.001$). When adjusted for age, several diseases (diabetes and CKD) and MS severity, mortality rates and HF hospitalisations still significantly differed from Period 1 to Period 4 (**Supplementary Fig. 1**). Notably, the group that underwent intervention displayed a rising composite outcome over time (log-rank test, $P = 0.007$) (**Fig. 4**).

DISCUSSION

In this large, multicentre, longitudinal follow-up study of 2,337 patients with rheumatic MS, we investigated the trends in clinical characteristics, treatment patterns, and clinical outcomes over 20 years. The average age of the patients with moderate or severe rheumatic MS increased significantly, with a rise in comorbidities such as hypertension, diabetes, and AF. Additionally, the proportion of mitral interventions within five years after diagnosis increased. MVR cases increased steadily; however, the proportion of PMV remained consistent. Clinical outcomes of rheumatic MS deteriorated over the 20 years, particularly relative to all-cause death and HF hospitalisation.

Although previously published studies have demonstrated a decline in the incidence of RHD in developed countries during the late 20th century,[1,14,15] the disease remains prevalent in developing countries, which are countries with a larger proportion of the global population[2]; However, recently published studies have shown a shift in the epidemiology of RHD in developing countries. In the last decade, new RHD cases in Brazil have decreased significantly, at least in larger urban centers. While in rural places, where medical treatment is less accessible, RHD is still common.[16] A further investigation in China revealed that out of

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a total of 8,929 patients diagnosed with VHD, only 365 individuals (4%) presented with either isolated MS or a mix of MS and mitral regurgitation (MR) that the vast majority of these showed rheumatic etiology.[17] Previous studies have focused primarily on changes in RHD prevalence and mortality rates over time, providing limited insight into the details of evolving characteristics of patients with the disease.

To our knowledge, this is the first study to comprehensively analyse the temporal trends in clinical characteristics, treatment patterns, and clinical outcomes of patients with rheumatic MS in a rapidly growing country that transitioned from a developing to a developed status over 20 years. The epidemiological observations in the Global Burden of Disease Study, based on 2019 data, show that the prevalence of RHD is increasing globally, but the mortality rate is decreasing.[18] Korea is classified as a non-endemic country having a significantly low incidence of RHD, with an age-standardised disability-adjusted life-years rate < 15.1.[18,19] RHD is not as frequently diagnosed in Korea as it was in past years; this might have contributed to the results of this registry differing from global diagnosis and mortality trends. Given the lack of information on the characteristics of rheumatic MS in other rapidly developing countries with increasing life expectancy, our findings have important implications for interpreting the disease trends. They may guide the development of effective management strategies in similar settings.

A significant trend that warrants discussion is the increasing age of patients with moderate or severe rheumatic MS; early disease detection is expected to become prevalent with improved medical accessibility and screening. Notably, with increased access to healthcare compared to the past years, younger age groups with early-stage disease may possibly experience a surge in diagnosis rates, akin to the bicuspid aortic valve population in Korea.[20,21] However, the average age of patients diagnosed with rheumatic MS has steadily risen, with a third of patients aged over 70 years. Furthermore, the severity of MS at initial diagnosis has advanced over time. The primary cause of this phenomenon is that some patients were affected in earlier decades but were only recently diagnosed. Conversely, the number of newly diagnosed patients with rheumatic fever decreased in Korea[6] because of improved hygiene, nutrition, and medical care accessibility. Additionally, the change in environment might have reduced the number of rheumatic fever reinfections; reinfections can lead to more rapid progression of valve deterioration. Furthermore, clinical experience in diagnosing RHD among medical personnel is decreasing over time because of the decreased overall number of cases or shifts in referral patterns to the four tertiary care hospitals occur; these factors may have changed the population of patients with RHD in this registry.

As the ageing population of rheumatic patients experiences more advanced stages of MS, there is a corresponding increase in comorbidities such as hypertension, diabetes, CKD, AF, and stroke. Additionally, over time, there is a higher prevalence of concomitant valvular dysfunction, including AS, AR, and TR, resulting from more advanced stages of rheumatic valve disease and the presence of degenerative valve diseases. These comorbidities can affect patient symptoms, treatment response, or prognosis.

The proportion of patients undergoing mitral intervention increased over time, with 47.5% receiving the intervention in the most recent period compared to 31.2% in the earliest period. This trend is likely due to the increased severity of rheumatic MS at diagnosis and better access to therapies over time with improved socioeconomic development. Notably, the rate of PMV remained similar over time, while the rate of MVR showed an increasing trend.

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This can be attributed to increased age at diagnosis of rheumatic MS over time. PMV is often considered a bridging therapy to delay MVR in younger patients with suitable valve morphology.[22-24] However, given that the mean age of rheumatic MS patients has risen from 51 to 60 years, MVR may be a more acceptable option for treating rheumatic MS. MVR is also a better treatment option for severe MR or multivalvular illness combined with MS, where PMV cannot be used.[24] The increasing prevalence of multivalvular disease may account for some of the increase in choosing MVR. The analyses of data from the Korea Heart Valve Surgery Registry (KHVSR) also showed increasing trends for complex procedures in valve surgery including MVR, and demonstrated remarkably low risks of operative mortality.[25] Last possible explanation for the decreasing rate of PMV could be the reduction in the number of experienced PMV centres. PMV requires a high level of expertise and should only be performed at centres with significant experience in the procedure.[22,23] A previous study showed that the number of PMV cases has decreased in the United States, and the risk of associated complications has increased.[26] The reduced number of centres with PMV-experienced specialists impacts the clinical outcomes and peri/post-procedural risks of PMV. As a result, patient groups that become more challenging to treat with PMV would be absorbed into the group treated with MVR.

While there has been a general improvement in treatment strategy, this study reveals a progressive deterioration in clinical outcomes for patients with rheumatic MS. The composite event, which includes all-cause mortality, HF admission, and stroke, has increased over time, irrespective of the treatment employed. The primary event driving the trend in the composite outcome was HF hospitalisation. We counted all hospital admission on echocardiography day as an event because the time between the study and admission date is commonly unclear in tertiary, referral centers. We deduced that that's why period 3 and period 4 HF admission exhibited a notable disparity from the very beginning. All-cause mortality rates and hospitalisation rates for HF tended to worsen even after adjustment for age and underlying comorbidities. In comparison, the incidence of stroke remained relatively stable throughout this period, possibly due to the increased use of anticoagulation therapy and an increased rate of mitral intervention.

As an observational study, we are limited in our causal analysis. But we cautiously assess that this trend, despite advances in treatment, may be due to the increasing number of older patients with mixed-type, severe forms of rheumatic MS with valve degeneration, multiple comorbidities. We are in treating a more challenging patient population in rheumatic MS.[27,28] Transcatheter MVR or PMV with an improved balloon system could be a future treatment option for such patients;[29] these minimally invasive approaches offer excellent safety and efficacy and can help address the evolving challenges the patient population experiences. Further research is needed to evaluate their efficacy and safety.

Our study has several limitations. First, it was conducted in a single country using retrospective data, leading to potential selection and referral biases and limited generalisability. For example, because of the limitations of a retrospective, observational study, there are some data points not being included. Socioeconomic factors, New York Heart Association Functional Classification, an information about coronary artery disease or bypass surgery, surgical risk assessment score (such as the Society of Thoracic Surgeons score or European System for Cardiac Operative Risk Evaluation II) or several laboratory data related to HF were not included in the study. Further documentation and analysis of this data will be required for phase II registry and future research. Second, it is challenging to establish causal

relationships of the association of certain factors and clinical events in an observational, retrospective study. Additional research should be designed to analyze precise cause. Third, in Period 4, cautious interpretation is required since the observation time may not have been long enough for disclosure of the clinical outcome. Fourth, national epidemic outbreaks (Middle East respiratory syndrome in 2015 and COVID-19 in 2019) may have altered clinical outcomes during the study period. According to additional analyses (supplement) without these periods, clinical outcomes between time periods remained significantly different. Lastly, early identification and eradication strategies for RHD are not covered in the study. Despite these limitations, this large registry study in South Korea provides valuable insights into the changing trends of rheumatic MS in developed nations over the past two decades.

In this multicentre study of patients with rheumatic MS, there was a significant increase in patient age, comorbidities, and valve disease severity as the country transitioned from a developing to developed status. Clinical outcomes deteriorated over 20 years, highlighting the need for less invasive procedures that consider age and comorbidities to improve patient outcomes.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Temporal trends for cumulative incidences of composite outcome (**A**), all-cause death (**B**), hospitalization for HF (**C**), and ischemic stroke (**D**) were estimated using the Kaplan–Meier method with adjustment of age, diabetes, and chronic kidney disease.

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