Epidemiology and treatment outcome of ANCA-associated vasculitis in South Korea: a nationwide, population-based cohort study

J.W. Park[1,3], J. Song[2], S. Choi[3], S.J. Park[2], S.M. Park[2,4], E.Y. Lee[1,3]

[1]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul;[2]Department of Biomedical Sciences, Seoul National University Graduate School, Seoul; [3]Department of Internal Medicine, Seoul National University Hospital, Seoul; [4]Department of Family Medicine, Seoul National University Hospital, Seoul, Republic of Korea.

Abstract

Objective

To investigate the epidemiological features of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in South Korea.

Methods

We identified the index cases of GPA and MPA using the 2010-2018 Korean National Health Insurance Service database and the Rare Intractable Disease registry for the entire Korean population. Each disease's incidence and prevalence rates and trends over time were analysed. To assess the impact of disease on morbidity and mortality, a comparator group comprising the general population was established using nearest-neighbour matching by age, sex, income, and comorbidity index, at a 5:1 ratio. Morbidity outcomes included the initiation of renal replacement therapy and admission to the intensive care unit.

Results

We identified 546 and 795 patients with GPA and MPA, respectively. The incidence rates of both diseases increased with age, with peak incidence rates observed among patients aged ≥70 years. The incidence of MPA increased continuously over time, whereas that of GPA showed no significant changes. During the observation period, 132 (28.7%) and 277 (41.1%) patients in the GPA and MPA groups, respectively, died, which were significantly higher than that in the general population (standardised mortality ratio: 3.53 and 5.58, respectively) and comparator group (hazard ratio: 4.02 and 5.64, respectively). Higher mortality and morbidity rates were observed among patients with MPA than among those with GPA.

Conclusion

In South Korea, the incidence of MPA has increased over time. Although both GPA and MPA had high rates of mortality and morbidity, MPA has a poorer prognosis than GPA.

Key words

ANCA-associated vasculitis, granulomatous with polyangiitis, microscopic polyangiitis, epidemiology

Jun Won Park, MD
Jihun Song, MS
Seulggie Choi, MD, PhD
Sun Jae Park, MS
Sang Min Park, MD, PhD
Eun Young Lee, MD, PhD

Please address correspondence to:
Sang Min Park
Department of Family Medicine,
Seoul National University Hospital,
101 Daehak-ro, Jongno-gu,
03080 Seoul, Republic of Korea
E-mail: smpark.snuh@gmail.com

and to:
Eun Young Lee
Division of Rheumatology,
Department of Internal Medicine,
Seoul National University Hospital,
101 Daehak-ro, Jongno-gu,
03080 Seoul, Republic of Korea.
E-mail: elee@snu.ac.kr

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Introduction

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are the two major types of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), a potentially life-threatening autoimmune disease that typically involves small-sized vessels (1). Although the accumulation of knowledge of the diagnosis and treatment of AAV has markedly improved treatment outcomes, it is still associated with a substantial rate of mortality and morbidity, poor quality of life, and economic burden on the patient (2-4).

Previous studies on AAV have reported geographical differences in the epidemiology and clinical features of GPA and MPA (5, 6). A comparative study of two population-based cohorts in the UK and Japan showed that MPA was the predominant type in Japan, whereas GPA was more common in the UK (7). Moreover, the clinical manifestations of AAV differ across various countries. For example, renal involvement in GPA is less frequent in Asian countries than in European ones (8). The prevalence of pulmonary involvement also differs across various countries (9-11). Furthermore, the reported AAV-related mortality and morbidity rates vary significantly across studies conducted in different geographical regions (2). These results suggest that establishing country-specific epidemiological data for GPA and MPA is necessary for physicians and healthcare systems to estimate the impact and burden of AAV. However, only a few studies have investigated the epidemiology of these diseases in South Korea.

Since 2006, the Korean National Health Insurance Service (NHIS) has maintained a longitudinal database of patients with rare intractable diseases (RID) and has collected all data on their medical use. This registry includes patients with GPA and MPA, allowing for an improved understanding of the epidemiology of these diseases in South Korea. Using this database, we aimed to investigate the incidence and prevalence of GPA and MPA and their trends over time. In addition, we analysed the prognosis of patients newly diagnosed with GPA and MPA to estimate the burden of these diseases on patients and the healthcare system.

Materials and methods

Data source

We used the Korean NHIS database, which covers the entire Korean population of >50 million individuals. The database includes longitudinal data on the demographics, diagnostic codes based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), medical procedures, prescription records, and types of medical utilisation of all Korean citizens. The NHIS database was accessed only for research purposes and analysed (research number of this study: NHIS-2022-1-752). All personally identifiable information in the database was removed to protect patient privacy. All patients diagnosed with GPA or MPA were simultaneously registered in the RID registry for reduced co-payments (12). To be registered in the RID registry, disease diagnosis must be confirmed by the treating physician according to the pre-specified diagnostic criteria legislated by the National Health Insurance (NHI). These criteria were based on the 1990 American College of Rheumatology (ACR) criteria for Wegener's granulomatosis and the 2012 Revised International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides for GPA and MPA, respectively. In South Korea, GPA and MPA have been included in the registry since 2009 and 2010, respectively.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB number: E-2102-076-1197). The need for patient consent was waived since all the data used in this study were anonymised.

Study population

Eligible patients were selected based on medical records in the hospital: ICD diagnosis codes for GPA (M31.3) or MPA (M31.7) and a RID code for GPA (V135) or MPA (V238) in the RID system (13). The index date was defined as

the date on which the ICD-10 and RID codes for MPA or GPA were first applied. Newly diagnosed patients with GPA or MPA were defined as those without a medical record of GPA or MPA before 31 December, 2009 and who were diagnosed with GPA or MPA between 01 January 2010, and 31 December 2018. Patients were allowed to enter the study cohort only once. To validate our algorithm, we searched our in-hospital database using the same methodology and identified patients with either GPA or MPA. Through this process, we identified 124 patients and confirmed the diagnosis. Patients with eligible ICD-10 codes who were not registered in the RID, were excluded to avoid a false inclusion of unconfirmed diagnoses of GPA or MPA in the study population. To assess potential bias, we searched our in-hospital database to determine the rate of confirmed diagnosis in these patients. Out of the 65 cases identified, only 3 were confirmed diagnosis of GPA or MPA. The final diagnosis of these patients is presented in Supplementary Table S1.

Data collection

Patients' age, sex, income levels (categorical; upper or lower levels), Charlson comorbidity index (CCI; continuous), smoking status (categorical; never-, former-, or current smokers), alcohol consumption (categorical; 0–1, 2–4, or 5–7 times per week), moderate-to-vigorous physical activity (MVPA, categorical; 0–2, 3–4, or 5–7 times per week), drug prescription (categorical; used or not used), body mass index (continuous; kg/m^2), systolic/diastolic blood pressure (continuous; mmHg), total cholesterol level (continuous; mg/dL), and serum fasting glucose level(continuous; mg/dL) were collected from the NHIS database. The income level (upper or lower) was derived from insurance premiums. The CCI was calculated annually based on the ICD-10 codes for major comorbidities (14). Data on smoking status, alcohol consumption, serum fasting glucose and total cholesterol levels, and MVPA were collected from participants who underwent the national health screening within 3 years before the index date.

Table I. Clinical features of the total patient with GPA and MPA.

	Patients with GPA	Patients with MPA
Number of people, n	546	795
Age [years], mean ± SD	60.0 ± 14.2	65.5 ± 13.2
Age [years], n (%)		
0-19	7 (1.3)	13 (1.6)
20-39	44 (8.1)	27 (3.4)
40-59	182 (33.3)	143 (18.0)
60-69	164 (30.0)	257 (32.3)
≥ 70	149 (27.3)	355 (44.6)
Sex, n (%)		
Male	255 (46.7)	354 (44.5)
Female	291 (53.3)	441 (55.5)
Income level†, n (%)		
Upper	331 (62.3)	504 (65.8)
Lower	200 (37.7)	262 (34.2)
Charlson comorbidity index, n (%)		
0	7 (1.3)	4 (0.5)
1-3	178 (32.6)	157 (19.8)
≥ 4	361 (66.1)	634 (79.8)
Initial immunosuppressive use, n (%)		
Glucocorticoid	511 (93.6)	752 (94.6)
Cyclophosphamide	270 (49.4)	392 (49.3)
Rituximab	48 (8.8)	114 (14.3)
Methotrexate	110 (20.2)	31 (3.9)
Azathioprine	114 (20.9)	196 (24.7)
Smoking status*, n (%)		
Never-smoker	208 (65.4)	323 (66.7)
Former-smoker	52 (16.4)	98 (20.2)
Current-smoker	58 (18.2)	63 (13.0)
Alcohol consumption* [times/week], n (%)		
0-1 (None and Light)	246 (77.4)	420 (86.8)
2-4 (Moderate)	54 (17.0)	52 (10.7)
5-7 (Heavy)	18 (5.7)	12 (2.5)
MVPA* [times/week], n (%)		
0-2	268 (84.3)	415 (85.7)
3-4	33 (10.4)	51 (10.5)
5-7	17 (5.4)	18 (3.7)
BMI[b] [kg/m^2], mean ± SD	23.84 ± 2.98	23.79 ± 3.11
Systolic BP* [mmHg], mean ± SD	124.8 ± 14.98	125.6 ± 15.49
Diastolic BP* [mmHg], mean ± SD	76.1 ± 9.35	75.5 ± 9.30
TC* [mg/dL], mean ± SD	190.3 ± 40.83	185.2 ± 36.40
FGS* [mg/dL], mean ± S**D**	103.1 ± 27.10	99.1 ± 22.4

p-values were calculated using the chi-squared test for categorical variables and analysis of variance for continuous variables.

†Study population: GPA (n=531) and MPA (n=766).

*Study population, who take national health screening: GPA (n=318) and MPA (n=484).

GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; n: number of patients; SD: standard deviation; MVPA: moderate and vigorous physical activity; BMI: body mass index; BP: blood pressure; TC: total cholesterol; FGS: fasting glucose serum.

History of drug prescription (used or not), including immunosuppressants, such as glucocorticoids, cyclophosphamide, rituximab, methotrexate (MTX), and azathioprine was collected. Initial immunosuppressive agents were defined as those prescribed within 3 months of the index date. Patients' causes and dates of death were collected from database of Statistics of Korea (KOSTAT), which contains complete data regarding the dates and causes of death based on ICD-10 codes.

Outcomes

The main outcomes were the annual incidence and prevalence rates of GPA and MPA during the follow-up period. The annual incidence rate was calculated as the number of cases per million persons. The total number of citizens in Korea was obtained from the Korean Statistical Information Service provided by KOSTAT and used for the calculations. The secondary outcomes included renal replacement therapy (RRT, including haemodialysis and

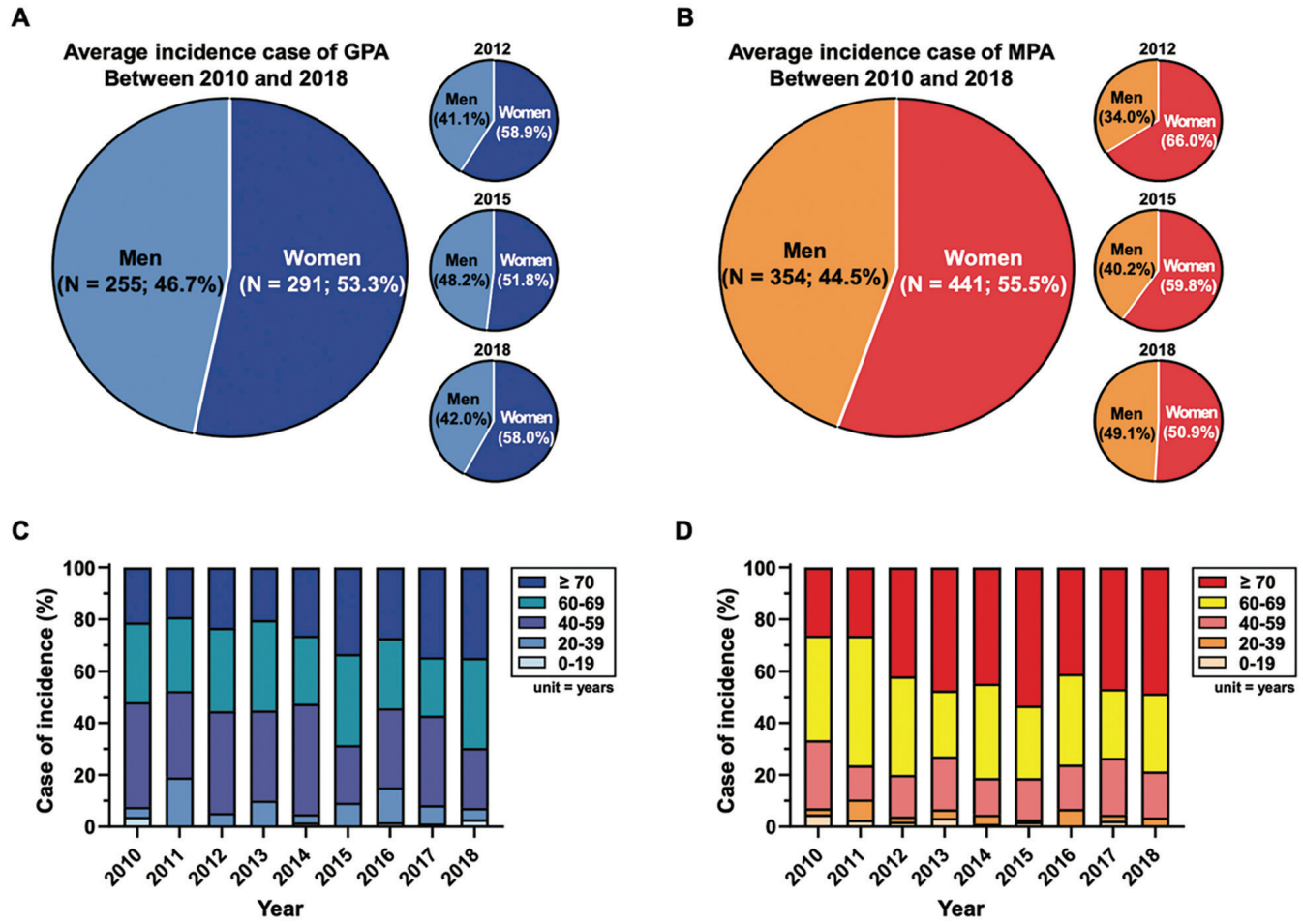

Fig. 1. Distribution of sex and age in the index cases of GPA (**A** and **C**) and MPA (**B** and **D**).

continuous renal replacement therapy), admission to the intensive care unit (ICU), and death from any cause. RRT and ICU admissions were identified using specific procedural codes (15-17).

Statistical analysis

All analyses were performed using the observed data, and no imputation of missing values was performed. The chi-square test for categorical variables and analysis of variance for continuous variables were used to determine statistical differences (two-tailed). To investigate the effects of GPA and MPA on the secondary outcomes, we established a comparator group representing the general population for each disease group, matched by age, sex, income, CCI, and index year. Nearest-neighbour matching was performed at a 5:1 ratio using a calliper of 0.2. Time-to-event outcomes between the two groups were compared using the Cox proportional hazards model. Standardised mortality ratios (SMRs) with 95% confidence intervals (95% CIs) were calculated and compared with the expected mortality in the general population.

All statistical analyses were performed using SAS software (v. 9.4; SAS Institute Inc., Cary, NC, USA), and statistical significance was determined at $p<0.05$.

Results

Study population and their clinical features

A total of 546 and 795 index cases of GPA and MPA were analysed to estimate the incidence and prevalence rates. In the analysis for secondary outcomes, patients who were unmatched with any of the comparator groups, those who died, and those underwent RRT, or were admitted to the ICU before the index date were excluded. Finally, 460 and 674 cases of GPA and MPA were analysed for secondary outcomes (Suppl. Fig. S1). Among the study population, 318 patients with GPA and 484 with MPA received national health screening within 3 years before the index date.

The baseline characteristics of the included patients on the index date are presented in Table I. The mean (SD) age of the patients was 60.0 (14.2) and 65.5 (13.2) years in the GPA and MPA groups, respectively. The number of patients with CCI ≥4 was 361 (66.1%) and 634 (79.8%) in the GPA and MPA groups, respectively.

The proportion of patients aged >70 years at the index date increased gradually over time in both groups; however, they were significantly higher in the MPA group (Fig. 1). Overall, both diseases were slightly more prevalent in women, with a male-to-female of 0.88 and 0.80 for GPA and MPA, respectively. The male-to-female ratio of index cases in the GPA group remained

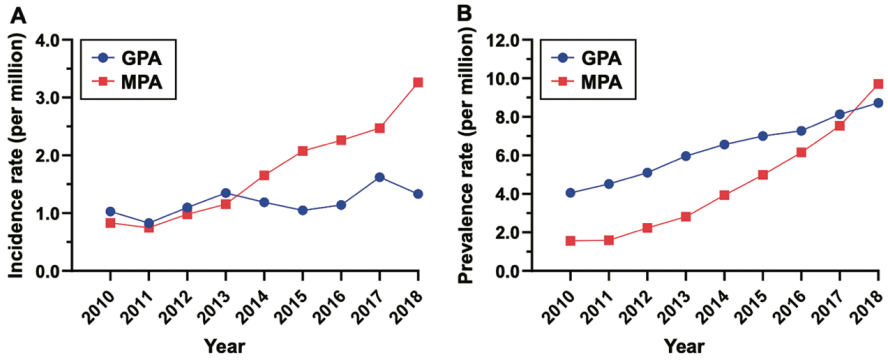

Fig. 2. Annual incidence (**A**) and prevalence (**B**) rates (per million) of GPA and MPA over time.

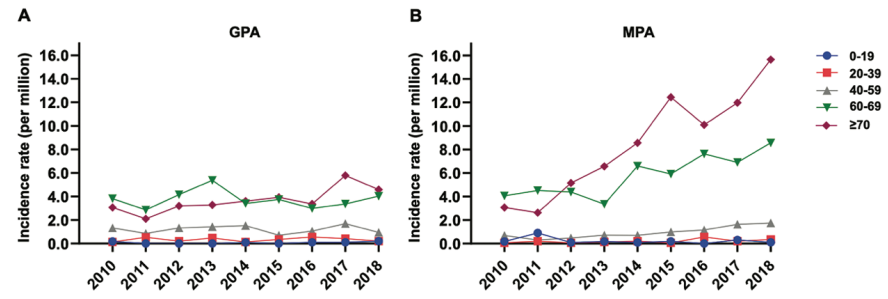

Fig. 3. Age-specific annual incidence rates of GPA (**A**) and MPA (**B**) over time.

stable over time. However, in the MPA group, it increased from 0.52 in 2012 to 0.96 in 2018 during the observation period.

Incidence of GPA and MPA

During the observation period, GPA and MPA showed different trends in incidence rates over time. In 2010, the annual incidence rates (per million) of GPA and MPA were 1.03 and 0.83, respectively. The incidence rate of MPA continuously increased over time to 3.26 in 2018, whereas the annual incidence rate of GPA did not significantly change during the observation period and was 1.33 in 2018 (Fig. 2). There was no seasonal variation in the incidence rates in either disease group (Suppl. Fig. S2). The annual incidence rates of GPA and MPA are presented in Supplementary Table S2.

The age-specific incidence of GPA and MPA showed a clear increase with age; the age-specific incidence rates of GPA and MPA were extremely low among those aged <20 and 20–39 years (<1 per million). The highest incidence rates of GPA and MPA were observed among those aged ≥70 years. The incidence rates of GPA for all age groups were relatively stable throughout the study period. In contrast, the incidence rates of MPA among those aged 60–69 and ≥70 years increased over time (Fig. 3). The peak annual incidence rates in these age groups were observed in 2018, which were 8.57 and 15.64 per million, respectively (Suppl. Table S3).

Prevalence of GPA and MPA

The annual prevalence rates (per million) of GPA and MPA continuously increased over time (Fig. 2 and Suppl. Table S2), with that of MPA increasing more rapidly. In 2010, the annual prevalence of GPA was higher than that of MPA (4.06 *vs.* 1.56); however, this trend was reversed in 2018 (8.72 *vs.* 9.71).

Treatment pattern of the study population

At 3 months after the index date, most patients (93.6% and 94.6% in the GPA and MPA groups, respectively) received glucocorticoids. Cyclophosphamide was prescribed to nearly half of the study population (49.4% and 49.3% in the GPA and MPA groups, respectively). In contrast, rituximab was initially prescribed to 48 (8.8%) and 114 (14.3%) patients in the GPA and MPA groups, respectively (Table I). The pattern of immunosuppressive treatment between the two groups was comparable, except for MTX, which was prescribed within 1 year of the index date

Table II. All-cause mortality in the included patients with GPA and MPA.

	Study population for GPA		*p*	Study population for MPA		*p*
	Control group (n=2,814)	GPA group (n=460)		Control group (n=4,056)	MPA group (n=674)	
All-cause death						
Event, n (%)	221 (9.4)	132 (28.7)		402 (11.9)	277 (41.1)	
Person-years	13,831	2,251		16,805	2,351	
Unadjusted HR (95% CI)	1.00 (Reference)	4.02 (3.09, 5.24)	<0.001	1.00 (Reference)	5.64 (4.06, 6.83)	<0.001
Adjusted HR (95% CI)						
Model 1	1.00 (Reference)	4.55 (3.50, 5.93)	<0.001	1.00 (Reference)	5.94 (4.90, 7.20)	<0.001
Model 2	1.00 (Reference)	5.15 (3.21, 8.28)	<0.001	1.00 (Reference)	8.62 (6.52, 11.4)	<0.001

Hazard ratios were calculated by Cox proportional hazards regression analysis adjusted for following covariates:
Model 1: age, sex, income level, and Charlson comorbidity index.
Model 2: Model 1 + drug prescription.
GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; n: number of patients.

Table III. Comparison of treatment outcome and prognosis between patients with GPA and MPA.

	Study population		*p*-value
	GPA (n=460)	MPA (n=674)	
Death			
Event, n (%)	132 (28.7)	277 (41.1)	
Person-years	2,251	2,351	
Unadjusted HR (95% CI)	1.00 (Reference)	1.81 (1.47, 2.23)	<0.001
Adjusted HR (95% CI)			
Model 1	1.00 (Reference)	1.33 (1.08, 1.65)	0.009
Model 2	1.00 (Reference)	1.33 (1.06, 1.68)	0.013
Renal replacement therapy			
Event, n (%)	95 (20.6)	287 (42.6)	
Person-years	2,019	1,778	
Unadjusted HR (95% CI)	1.00 (Reference)	2.47 (1.96, 3.12)	<0.001
Adjusted HR (95% CI)			
Model 1	1.00 (Reference)	2.05 (1.61, 2.61)	<0.001
Model 2	1.00 (Reference)	1.68 (1.31, 2.15)	<0.001
ICU admission			
Event, n (%)	127 (27.6)	261 (38.7)	
Person-years	1,972	2,000	
Unadjusted HR (95% CI)	1.00 (Reference)	1.67 (1.35, 2.07)	<0.001
Adjusted HR (95% CI)			
Model 1	1.00 (Reference)	1.38 (1.10, 1.72)	0.005
Model 2	1.00 (Reference)	1.34 (1.06, 1.69)	0.014

Hazard ratios were calculated by Cox proportional hazards regression analysis adjusted for following covariates:
Model 1: age, sex, income level, and Charlson comorbidity index.
Model 2: Model 1 + drug prescription.
n: number of patients; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; HR: hazard ratio; CI: confidence interval; ICU: intensive care unit.

to 149 (28.1%) and 48 (6.3%) patients in the GPA and MPA groups, respectively (p<0.001) (Suppl. Fig. S3).

Treatment outcome and prognosis

During the observation period, the all-cause mortality rate was 28.7% (n=132) and 41.1% (n=277) in the GPA and MPA groups, respectively, whereas it was it was 9.4% (n=221) and 11.9% (n=402) in each comparator group, respectively. GPA and MPA groups showed significantly higher mortality rates, with unadjusted hazard ratio (HR) of 4.02 (3.09–5.24) and 5.64 (4.06–6.83), respectively. This result did not change following multivariable analysis adjusted for patient age, sex, comorbidities, and concomitant medications (Table II). In addition, these results were also consistent with the sensitivity analysis results in which smoking status, alcohol consumption, MVPA level, and serum fasting serum glucose/cholesterol levels were further adjusted in the national health screening sub-cohort (Suppl. Table S4). Moreover, the SMRs of the GPA and MPA groups showed consistent results (3.53 [2.96–3.86] in the GPA group and 5.58 [4.95–6.27] in the MPA group).

Although all-cause mortality rates in both groups were significantly higher than that in each comparator group, it was higher in the MPA group than in the GPA group (unadjusted HR 1.81 [1.47 to 2.23], p<0.001; Table III). In both groups, all-cause mortality occurred most frequently during the first year after the index date (48.9% and 58.3% in the GPA and MPA groups, respectively).

Patients in the GPA and MPA groups showed a significantly higher risk of RRT and ICU admission than those in the comparator groups (Suppl. Fig S4). Similar to all-cause mortality, these risks were significantly higher in the MPA group (Table III). Among the index MPA cases, 287 (42.6%) patients received RRT, most of which occurred shortly after the index date.

Discussion

Investigating the epidemiological features of rare diseases is an important step in establishing treatment strategies to be employed by physicians and the healthcare system. However, it is a challenging task which requires a large population for precise estimation. The universal healthcare insurance system and the linked RID database allow us to capture all registered cases of MPA and GPA in South Korea and, therefore, draw a robust conclusion on the incidence, prevalence, and outcome of the diseases.

We showed that the incidence rates of GPA and MPA during the study period were lower than those reported in previous epidemiological studies conducted in European countries (18, 19). Few studies have investigated AAV incidence in Asian countries. A nationwide epidemiological study conducted in Taiwan showed that the incidence of GPA between 1997 and 2008 was only 0.37 per million (20). In contrast, another population-based study performed in Miyazaki Prefecture, Japan, showed that the incidence of MPA was 18.2 (95% CI 14.3–22.0) per million, based on 86 incidence cases of AAV (21). Since the incidence rate can be affected by many factors, such as the population structure and methodology used for case detection, a direct comparison of the incidence rates among various studies would be inappropriate. However, these studies, as well as the present study, showed that MPA has a significantly higher incidence rate than GPA, suggesting that racial differences and genetic backgrounds may determine the predominant AAV phenotype (22).

A few previous studies investigated the epidemiology of AAV in South Korea using the NHIS database. Among these, Ahn *et al*. examined the secular incidence and prevalence trends of AAV in South Korea (23). Their investigation showed a constant increase in the annual incidence of AAV from 2002 to 2018. However, a comprehensive analysis of the longitudinal incidence of each AAV subtype over time was lacking in their study. Interestingly, we demonstrated that in South Korea, GPA and MPA have different epidemiologic features

(24-26). Compared to GPA, the incidence rate of MPA increased continuously during the observation period; however, the exact cause is not clear. However, in South Korea, MPA was integrated into the RID system in 2010, which could have potentially contributed to the observed increase in the reported incidence due to increased case detection. Additionally, a prominent increase in the proportion of elderly (aged ≥65 years) patients with MPA was observed, from 10.8% in 2010 to 15.7% in 2020. This demographic shift may offer insights into explaining our findings.

Our results also showed that both GPA and MPA had significant effects on patient prognosis. Notably, patients with MPA showed a poorer prognosis than those with GPA; the all-cause mortality rate was significantly higher in the MPA group, and more than 40% of the patients underwent RRT shortly after diagnosis. Previous epidemiological studies have also shown that old age and decreased renal function were the most critical factors influencing increased mortality rate, which is consistent with our results (27, 28). As these factors were more prevalent in patients with MPA, they could partly explain the higher mortality rate in the group.

We also showed the initial pattern of use of immunosuppressants in the study population. Notably, cyclophosphamide was the most commonly used nonsteroidal inductive therapeutic agent for treating vasculitis, and nearly half of the study population received cyclophosphamide as the initial immunosuppressive treatment. This feature differs from that of previous studies performed using the RISE registry, which showed that the prescription rate of cyclophosphamide was only 7% (29). Although the RAVE trial showed that rituximab was not inferior to cyclophosphamide for severe AAV, its use for inductive therapy in patients with GPA or MPA was only authorised in South Korea after 2012 (30), which partly contributed to the treatment patterns observed in this study. Interestingly, in the GPA group, 20.2% of patients received MTX during the initial 3 months following the index date, which may indicate that GPA is less severe at diagnosis in a substantial proportion of patients with GPA in South Korea, whereas only 3.9% of the patients with MPA received MTX, suggesting the severity of MPA South Korean patients.

This study had some limitations. First, the database used in this study did not have information regarding disease activity, the reason for the prescription of specific medications, and the exact cause of death; therefore, the difference in treatment patterns according to the severity of vasculitis and treatment outcome could not be thoroughly investigated. In addition, since the NHIS database includes only claim data of prescribed medication authorised by the national healthcare system, an off-label use of rituximab could not be considered in this study. Second, although registration in the RID system in South Korea should be confirmed by the treating physician, some cases may have been misclassified, leading to biased results. However, using the electronic medical records database of our hospital, we showed that patients with the ICD-10 code for GPA or MPA who were not registered in the RID system did not have the disease. Third, in South Korea, the introduction of rituximab for the treatment of AAV in 2012 may have impacted treatment outcomes. Nevertheless, due to a lack of relevant data, we did not analyse the longitudinal trend of the outcomes. Finally, patients with fulminant GPA and MPA may expire before they are registered in the RID system and thus could not be included in this study.

In conclusion, this nationwide cohort study provided comprehensive epidemiological information on MPA and GPA in South Korea. The incidence rate of MPA is increasing, mainly in older patients, whereas that of GPA has remained stable over time. Although the risk of mortality and morbidity was significantly higher in the GPA and MPA groups than in the comparator groups, it was more prominent in the MPA group, with a mortality rate of approximately 40%. These results will play an important role in understanding the epidemiology of these diseases and establishing related national healthcare policies.

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