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ORIGINAL ARTICLE

Clinical role of albumin to globulin ratio in microscopic polyangiitis: a retrospective monocentric study

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Abstract

We investigated whether albumin to globulin ratio (AGR) at diagnosis may be associated with all-cause mortality in immunosuppressive drug-naïve patients with microscopic polyangiitis (MPA). We retrospectively reviewed the medical records of 88 MPA patients, who were first classified and in whom medications was first initiated in our tertiary Hospital. We collected clinical and laboratory data as well as the rate of all-cause mortality. AGR at diagnosis was calculated as a ratio of serum albumin over globulin fraction (protein–albumin). We compared variables between survived and deceased patients. The multivariable Cox hazard model was conducted to appropriately obtain the hazard ratios (HRs). The mean age at diagnosis was 56.3 years and 24 patients (27.3%) were men. Seven patients died for the mean follow-up period of 49.7 months. Deceased patients were elder than survived patients ($P = 0.048$). Five factor score (FFS) (2009) ($P = 0.001$), creatinine ($P = 0.026$) and AGR ($P = 0.007$) at diagnosis in deceased patients were higher than those in the survived. In the multivariable Cox hazard model analysis, only AGR at diagnosis (HR 0.004) was inversely associated with all-cause mortality during the follow-up. Furthermore, when the cutoff of AGR for death was set as 0.88, patients with AGR ≤ 0.88 exhibited the lower cumulative patients survival rate than those with AGR > 0.88 ($P = 0.006$). Among the conventional and MPA-related risk factors for mortality, AGR at diagnosis is inversely associated with all-cause mortality during follow-up in MPA patients.

Keywords Albumin to globulin ratio · All-cause mortality · Microscopic polyangiitis

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of three systemic vasculitides involving small vessels from capillaries to intraparenchymal arterioles and venules: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. Of three variants of AAV, MPA mainly induces rapid progressive necrotising glomerulonephritis, and it occasionally provokes pulmonary capillaritis or alveolar haemorrhage [1, 2]. Three previous studies regarding Korean patient with MPA reported the rate of all-cause mortality ranging from 7.7 to 55.6%. They provided several risk factors at diagnosis for all-cause mortality: among MPA-related risk factors, diffuse alveolar haemorrhage, heart and lung involvements, vasculitis activity and prognostic factors at diagnosis were suggested and among conventional risk factors, age at diagnosis was indicted [3–5].

Albumin is often decreased under the medical conditions such as severe liver disease, serious malnutrition and chronic inflammation and protein-losing nephropathy, while globulin fraction is mainly increased in cases of infection, chronic inflammation, immunoglobulin-producing haematological malignancies and autoimmune diseases [6, 7]. With these concepts, an index of albumin to globulin ratio (AGR) has been introduced and widely used to predict the poor outcome of cancers as well as all-cause mortality in non-cancer diseases [8–10]. Particularly, chronic inflammation can both reduce serum albumin and enhance globulin fraction concentration in

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the peripheral circulation, leading to a remarkable decrease in AGR.

Given that the initial AGR is associated with all-cause mortality in quite a few diseases, we assume that AGR at diagnosis might predict all-cause mortality in patients with MPA. However, to the best of our knowledge, there was no study on the association of AGR with all-cause mortality in patients with MPA to date. Thus, in this study, we investigated whether AGR at diagnosis of MPA may be associated with all-cause mortality in 88 immunosuppressive drug-naïve patients with MPA.

Materials and methods

Patients

We retrospectively reviewed the medical records of 88 patients with MPA based on the inclusion criteria as follows: (i) patients who were first classified as MPA from October 2000 to October 2017 at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital; (ii) patients who fulfilled the modified classification criteria for MPA by the algorithm suggested by the European Medicines Agency in 2007, in which authors added the modified contents of the Chapel Hill Consensus Conferences (CHCC) Nomenclature of Vasculitis proposed in 2012 [1, 2]; (iii) patients who had been followed up for 6 months or greater; (iv) patients who had well-documented medical records to assess clinical manifestations at diagnosis and calculate vasculitis activity score represented by Birmingham vasculitis activity score (BVAS) and prognostic factors identified by five factor score (FFS (2009)) at diagnosis [11, 12]; (v) patients who had the results of perinuclear (P)-ANCA and cytoplasmic (C)-ANCA or myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA at diagnosis [13]; (vi) patients who had no medical condition to interfere the classification of MPA identified by the 10th revised International Classification of Diseases (ICD-10); (vii) patients who had never received drugs for those medical conditions or (viii) immunosuppressive drugs prior to or at diagnosis, which were searched by the Korean Drug Utilisation Review (DUR) system. We clarified the inclusion criteria in Fig. 1.

Clinical and laboratory data

We obtained age and gender at the time of diagnosis of MPA. BVAS and FFS (2009) at diagnosis were calculated on the basis of the medical records. We collected laboratory results at diagnosis including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as were described in Table 1. We defined the follow-up duration as the period from diagnosis to the last visit in survived patients, while we defined it as the period from diagnosis to death in deceased patients. Among comorbidities enhancing the rate of all-cause mortality in the general population, hypertension, chronic kidney disease, end stage renal disease, ischaemic heart disease, congestive heart failure, interstitial lung disease and cerebrovascular disease were excluded, for they are items of BVAS [11, 14]. Therefore, in this study, comorbidities of MPA included only diabetes mellitus (DM), dyslipidaemia and obesity (body mass index (BMI) > 30). AGR at diagnosis was calculated as a ratio of serum albumin (g/dL) over globulin fraction (protein–albumin) (g/dL) [7].

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number and the percentage. Significant difference in categorical variables between the two groups were analysed by the chi-square test and Fisher's exact test. Significant differences in continuous variables between the two groups were compared by the Mann-Whitney test. The odds ratio (OR) was assessed using the multivariable logistic regression analysis of variables with P values less than 0.05 on the univariable logistic regression analysis. The multivariable Cox hazard model using variables with statistical significance in the univariable Cox hazard model was conducted to appropriately obtain the hazard ratios (HRs) during the considerable follow-up duration. The optimal cutoff of AGR for death was extrapolated as 0.88 by calculating the receiver operator characteristic curve (ROC) and selecting the maximised sum of sensitivity and specificity. Comparison of cumulative patient survivals between the two groups were analysed by the Kaplan-Meier survival analysis. P values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline characteristics are shown in Table 1. The mean age at diagnosis was 56.3 years and 24 patients (27.3%) were male. The mean follow-up period was 49.7 months. Seventy-

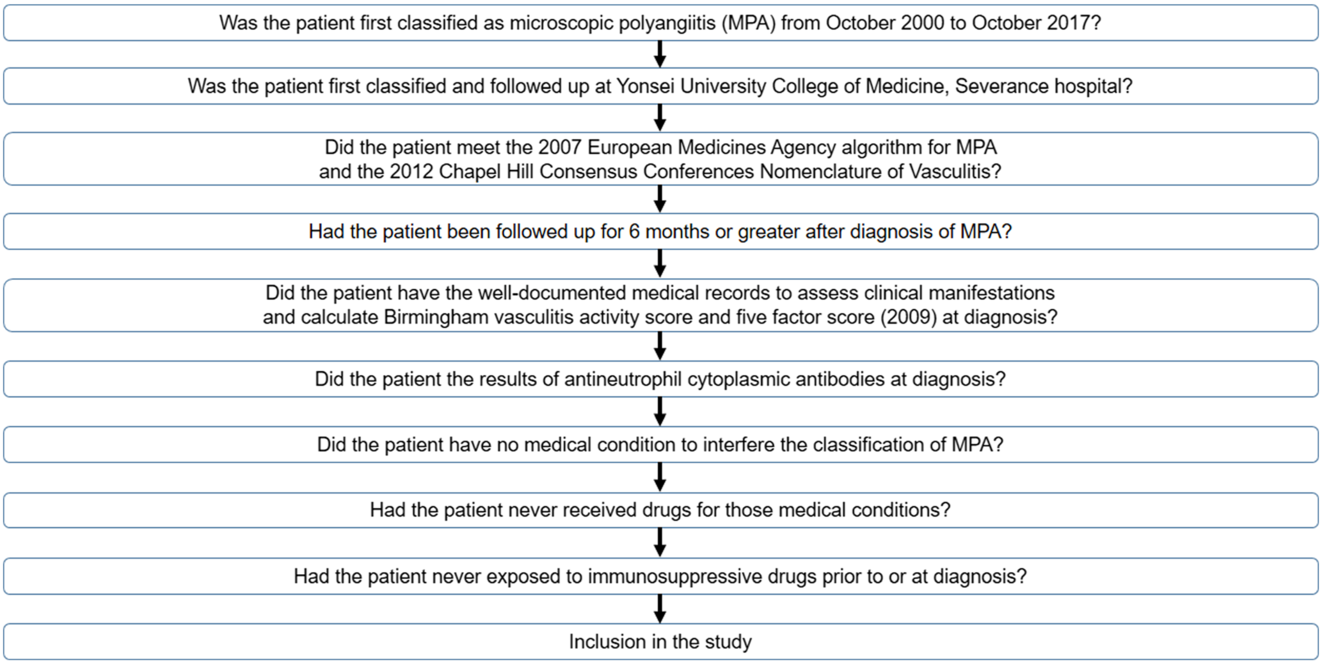

Fig. 1 Algorithm for inclusion criteria

five (85.2%) had ANCA (74 had MPO-ANCA (or P-ANCA), 5 had PR3-ANCA (or C-ANCA), 4 had both ANCAs and 13 had no ANCAs). The mean BVAS and FFS (2009) at diagnosis were 14.8 and 1.4, respectively, and 44.3% of patients had FFS (2009) at diagnosis ≥ 2. The mean initial ESR and CRP were 62.0 mm/h and 37.7 mg/L. The mean AGR at diagnosis was 1.2. We compared AGR at diagnosis between patients with and without each item of BVAS. Patients with general manifestations ($N = 47$) exhibited the lower mean AGR than those without ($N = 41$) (1.1 vs. 1.3, $P = 0.016$). Whereas, patients with muco-membranous and ocular manifestations ($N = 8$) exhibited the higher mean AGR than those without ($N = 84$) (1.4 vs. 1.2, $P = 0.034$) (Supplementary Table 1).

Comparison variables at diagnosis between survived and deceased patients

Deceased patients were elder than survived patients (66.7% vs. 55.4%, $P = 0.048$). The mean FFS (2009) at diagnosis and the number of patients having FFS (2009) at diagnosis ≥ 2 in deceased patients were greater than those in survived patients (2.6 vs. 1.3, $P = 0.001$ and 85.7% vs. 40.7%, $P = 0.022$). Deceased patients exhibited the higher mean creatinine and the lower serum albumin than survived patients (3.9 vs. 1.9, $P = 0.026$ and 2.8 vs. 3.6, $P = 0.011$) at the time of diagnosis. There were no significant differences in ESR and CRP at diagnosis between survived and deceased patients.

AGR at diagnosis in deceased patients was significantly lower than that in survived patients (0.9 vs. 1.2, $P = 0.007$) (Table 1). There were no significant differences immunosuppressive drugs administered during the follow-up of MPA between the two groups (Supplementary Table 2).

Multivariate logistic regression analysis

In comparison analysis, age, FFS (2009) ≥ 2, creatinine and AGR at diagnosis exhibited significant differences between survived and decreased patients, and they were included in the multivariable logistic regression analysis. Serum albumin was excluded, as it is one of the variables of the equation of AGR. Among four variables, only creatinine at diagnosis was remarkably associated with all-cause mortality (OR 1.450, 95% confidence interval (CI) 1.015, 2.074) (Table 2).

Cox hazard model analysis

In the univariable Cox hazard model analysis, age, male gender, BVAS, creatinine, alanine aminotransferase, total bilirubin and AGR at diagnosis were exhibited significant HRs. In the multivariable analysis, only AGR at diagnosis (HR 0.004, 95% CI 0.000, 0.644) was inversely associated with all-cause mortality during the follow-up (Table 3).

Relative risk of death and cumulative patient survival rate according to AGR $\leq$ 0.88

When we classified MPA patients into two groups according to the cutoff of AGR for death, patients with AGR ≤ 0.88 (5 of

Table 1 Baseline characteristics and comparison of variables at diagnosis between survived and deceased patients with MPA

Variables	All patients (*N* = 88)	Survived patients (*N* = 81)	Deceased patients (*N* = 7)	*P* value
Demographic data				
Age (year old) at diagnosis	56.3 ± 14.6	55.4 ± 14.6	66.7 ± 11.1	0.048
Male gender (*N*, (%))	24 (27.3)	20 (24.7)	4 (57.1)	0.064
Follow-up period (months)	49.7 ± 47.9	47.2 ± 46.6	79.2 ± 56.6	0.089
ANCA positivity (*N*, (%))	75 (85.2)	68 (84.0)	7 (100)	0.251
Activity and prognostic factor				
BVAS	14.8 ± 7.6	14.5 ± 7.5	19.7 ± 8.1	0.072
FFS (2009)	1.4 ± 1.0	1.3 ± 1.0	2.6 ± 0.8	0.001
FFS (2009) ≥ 1	68 (77.3)	61 (75.3)	7 (100)	0.135
FFS (2009) ≥ 2	39 (44.3)	33 (40.7)	6 (85.7)	0.022
Laboratory results				
White blood cell (/mm^3)	9121.0 ± 3737.0	8904.4 ± 3570.5	11,627.1 ± 4955.1	0.064
Haemoglobin (g/dL)	10.9 ± 2.4	11.0 ± 2.4	9.6 ± 1.7	0.128
Platelet × 10^3 (/mm^3)	314.7 ± 133.1	312.8 ± 133.0	336.0 ± 143.0	0.661
Fasting glucose (mg/dL)	116.4 ± 43.4	115.2 ± 41.4	130.6 ± 64.7	0.371
Blood urea nitrogen (mg/dL)	30.2 ± 28.4	28.4 ± 28.1	50.2 ± 25.1	0.052
Creatinine (mg/dL)	2.1 ± 2.2	1.9 ± 2.1	3.9 ± 2.8	0.026
Total protein (g/dL)	6.7 ± 0.9	6.7 ± 0.9	6.0 ± 0.9	0.063
Serum albumin (g/dL)	3.5 ± 0.8	3.6 ± 0.8	2.8 ± 0.6	0.011
Alkaline phosphatase (IU/L)	87.0 ± 82.3	81.8 ± 56.0	147.1 ± 227.6	0.477
Aspartate aminotransferase (IU/L)	24.8 ± 31.1	22.6 ± 17.9	51.1 ± 94.0	0.452
Alanine aminotransferase (IU/L)	22.2 ± 36.2	18.8 ± 17.7	60.9 ± 113.8	0.366
Total bilirubin	0.7 ± 1.9	0.5 ± 0.3	2.9 ± 6.7	0.381
Acute reactants				
ESR (mm/h)	62.0 ± 38.8	60.6 ± 39.1	77.9 ± 34.5	0.261
CRP (mg/L)	37.7 ± 51.4	37.3 ± 53.1	42.7 ± 24.5	0.792
Albumin to globulin ratio (AGR)	1.2 ± 0.4	1.2 ± 0.4	0.9 ± 0.2	0.007
Comorbidities except items of BVAS at diagnosis (*N*, (%))				
DM	20 (22.7)	17 (21.0)	3 (42.9)	0.185
Dyslipidaemia	46 (52.3)	40 (49.4)	6 (85.7)	0.065
Obesity	8 (9.1)	7 (8.6)	1 (14.3)	0.627

Values are expressed as mean ± standard deviation and number (*N*) (%)

MPA microscopic polyangiitis, *BVAS* Birmingham vasculitis activity score, *FFS* five factor score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DM* diabetes mellitus

Table 2 Multivariable logistic regression analysis of variables at diagnosis of MPA associated with all-cause mortality

Variables	Odds ratio	95% confidence interval	*P* value
Age (year old) at diagnosis	1.038	0.935, 1.152	0.488
FFS(2009) ≥ 2	3.596	0.297, 43.526	0.314
Creatinine	1.450	1.015, 2.074	0.041
*Serum albumin**	*N/A*	*N/A*	*N/A*
Albumin to globulin ratio (AGR)	0.079	0.003, 2.075	0.128

MPA microscopic polyangiitis, *FFS* five factor score

*Serum albumin, which are items of the equation of albumin to globulin ratio, were not included in multivariable analysis

Table 3 Univariable and multivariable Cox hazard model analyses of variables for all-cause death in MPA patients during the follow-up ($N = 88$)

Variables at diagnosis	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Demographic data at diagnosis						
Age	1.100	1.013, 1.195	0.024	1.123	0.971, 1.300	0.119
Male gender	6.967	0.026, 0.795	0.026	36.595	0.917, 1460.171	0.056
ANCA positivity at diagnosis	45.476	0.031, 67,237.236	0.305			
Activity and prognostic factor						
BVAS	1.112	1.008, 1.228	0.035	1.058	0.797, 1.402	0.698
FFS(2009) ≥ 2	7.968	0.953, 66.610	0.055			
Laboratory results at diagnosis						
White blood cell	1.000	1.000, 1.000	0.217			
Haemoglobin	0.745	0.496, 1.117	0.154			
Platelet	1.002	0.997, 1.007	0.508			
Fasting glucose	1.009	0.997, 1.021	0.146			
Blood urea nitrogen	1.009	0.995, 1.023	0.208			
Creatinine	1.331	1.024, 1.730	0.032	1.396	0.797, 2.445	0.244
*Protein**	*0.473*	*0.201, 1.116*	*0.088*			
*Serum albumin**	*0.184*	*0.046, 0.742*	*0.017*			
Alkaline phosphatase	1.004	1.000, 1.008	0.076			
Aspartate aminotransferase	1.009	0.999, 1.020	0.078			
Alanine aminotransferase	1.008	1.000, 1.016	0.043	0.976	0.893, 1.066	0.584
Total bilirubin	1.150	1.007, 1.314	0.040	1.360	0.332, 5.735	0.676
Acute reactants at diagnosis						
ESRs	1.018	0.996, 1.040	0.117			
CRP	1.005	0.987, 1.023	0.580			
Albumin to globulin ratio (AGR)	0.019	0.000, 0.752	0.035	0.004	0.000, 0.644	0.033
Comorbidities except clinical manifestations of BVAS at diagnosis*						
DM	4.313	0.847, 21.955	0.078			
Dyslipidaemia	2.871	0.334, 24.657	0.336			
Obesity	3.253	0.332, 31.830	0.311			
Medications administered during the follow-up						
Glucocorticoid	25.776	0.001, 518,587.302	0.520			
Cyclophosphamide	3.219	0.664, 15.612	0.147			
Mycophenolate mofetil	1.870	0.206, 16.985	0.578			
Azathioprine	0.516	0.060, 4.452	0.547			
Tacrolimus	0.041	0.000, 45,166.054	0.653			
Rituximab	0.040	0.000, 16,918.003	0.627			
Methotrexate	0.046	0.000, 3,307,595.669	0.738			

MPA microscopic polyangiitis, *BVAS* Birmingham vasculitis activity score, *FFS* five factor score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DM* diabetes mellitus

*Total protein and serum albumin, which are items of the equation of albumin to globulin ratio, were not included in multivariable analysis

24 patients) exhibited the higher rate of death than those with AGR > 0.88 (2 of 64 patients) ($P = 0.006$). Furthermore, patients with AGR ≤ 0.88 had a significantly higher relative risk of death than those without (RR 8.518) (Fig. 2a).

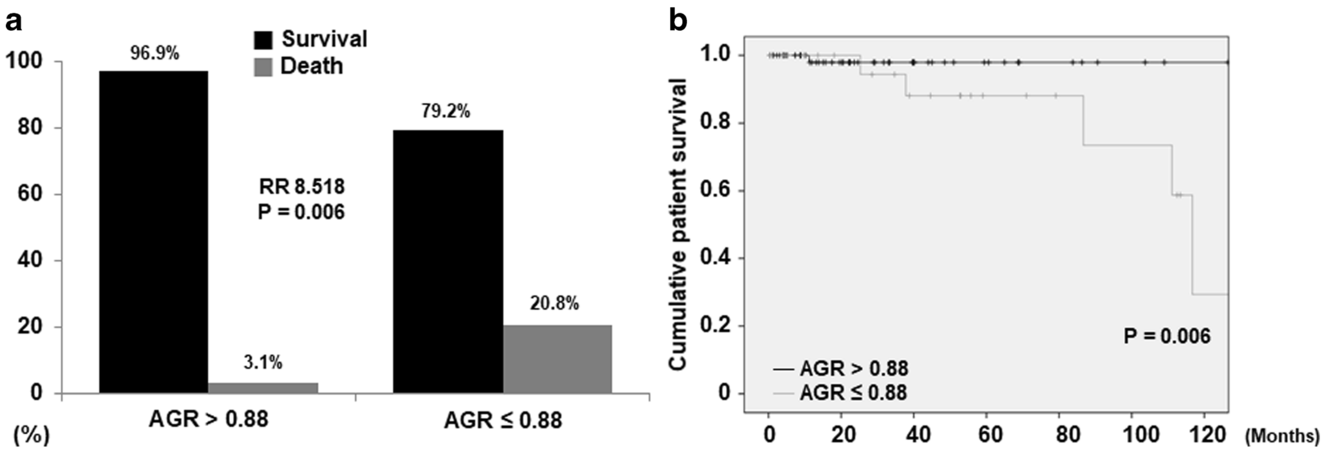

Fig. 2 Relative risk of death and cumulative patient survival rate according to AGR ≤ 0.88. Among 24 patients with AGR ≤ 0.88, 5 patients died and among 64 patients with AGR > 0.88, only 2 patients died (20.8% vs. 3.1%) (**a**). During the follow-up, patients with AGR ≤ 0.88 exhibited the lower cumulative patient survival rate than those with AGR > 0.88 (P = 0.006) (**b**)

Cumulative patient survival rate was shown in Fig. 2b. During follow-up, patients with AGR ≤ 0.88 exhibited the lower cumulative patient survival rate than those with AGR > 0.88 (P = 0.006).

Discussion

In this study, we demonstrated that AGR at diagnosis was inversely associated with all-cause mortality in immunosuppressive drug-naïve patients with MPA. Particularly, the multivariable Cox hazard model analysis using conventional risk factors for mortality and MPA-related variables with significance in the univariable analysis elucidated that only AGR at diagnosis was meaningfully associated with all-cause mortality during the follow-up. The multivariable logistic regression analysis does not include the follow-up period, in other words, the disease duration, which must be one of generally agreed MPA-related risk factors for all-cause mortality. By contrast, the Cox hazard model analysis needs the follow-up period as an essential variable and is more useful to determine the mortality rate during the follow-up than logistic regression analysis. In addition, we extrapolated the optimal cutoff of AGR for death as 0.88 by calculating the ROC and compared cumulative patient survivals between patients with AGR ≤ 0.88 and those with AGR > 0.88. We demonstrated that patients with AGR ≤ 0.88 had a significantly higher relative risk of death than those without (RR 8.518) and furthermore, patients with AGR ≤ 0.88 exhibited the lower cumulative patients survival rate than those with AGR > 0.88 (P = 0.006). Therefore, we believe that the present study can contribute to developing a novel index to predict all-cause mortality in MPA patients as a pilot study.

In this study, we included conventional risk factors such as age, male gender, DM, dyslipidaemia and obesity. Other conventional risk factors in the general population were excluded, as they are included in the items of BVAS [11, 14]. Both age and male gender were associated with all-cause mortality, while DM, dyslipidaemia and obesity were not. In terms of DM, the 2010 prevalence of type 2 DM in 50–59-year-old men was 12.3% and that of women was 7.7% in Korea. Also the 2010 prevalence of type 2 DM in 60–69-year-old men was 19.2% and that of women was 17.4% in Korea [15]. In this study, the prevalence of type 2 DM was 22.7% with the mean age of 56.3 years old at diagnosis and this result was higher than that in the general population. We assume that DM in MPA patients might be controlled with a regular check-up more strictly than the general population, leading to minimising the contribution of DM to all-cause mortality. No association between dyslipidaemia and all-cause mortality may be also understood by the same hypothesis. The 2010 prevalence of obesity (BMI ≥ 30 kg/m^2) in Koran population was 1.5% [16], while that in our study, population was as high as 9.1%. Nevertheless, obesity did not affect the mortality rate in MPA patients.

We set BVAS, FFS (2009), ESR, CRP at diagnosis and medications administered as MPA-related risk factors for all-cause mortality. In our previous study, we demonstrated that FFS at diagnosis more than 2 and diffuse alveolar haemorrhage could predict all-cause mortality in patients with all MPA [5]. In this study, among these factors, only BVAS at diagnosis was associated with all-cause mortality. FFS at diagnosis ≥ 2 showed a potential to contribute to all-cause mortality, but there was no statistical significance. We assume that this discrepancy might be due to the small number of deceased patients and the different study population, which was confined to MPA patients.

Our study has two advantages. First, we provided concrete results on the association between AGR at diagnosis and all-cause mortality in a considerable number of patients with MPA. Second, the classification of MPA and the initiation of immunosuppressive drug was done in a single centre, which can minimise the inter-centric variation. However, our study also has several issues. First, our study was designed as a retrospective study, so we could not strictly control the conventional and MPA-related risk factors for all-cause mortality. Second, because the number of MPA patients, particularly deceased patients, was not large to estimate the rate of all-cause mortality in all patients with MPA. We hope that the future prospective and cohort-based studies with the larger number of patients will provide the more valuable and precise information on the association of AGR at diagnosis with all-cause mortality during the follow-up in patients with MPA.

Conclusions

Among the conventional and MPA-related risk factors for mortality, AGR at diagnosis is inversely associated with all-cause mortality during the follow-up of 6 months or greater in patients with MPA.

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Compliance with ethical standards

This study was approved by the institutional Review Board (IRB) of Severance Hospital (4-2017-0673), and the patient's written informed consent was waived by the approving IRB, as this was a retrospective study.

Disclosures None.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CGM, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DGI, Specks U, Stone JH, Takahashi K, Watts RA (2013) 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65(1):1–11
2. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D (2007) Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 66(2):222–227
3. Oh JS, Lee CK, Kim YG, Nah SS, Moon HB, Yoo B (2009) Clinical features and outcomes of microscopic polyangiitis in Korea. J Korean Med Sci 24(2):269–274
4. Ahn JK, Hwang JW, Lee J, Jeon CH, Cha HS, Koh EM (2012) Clinical features and outcome of microscopic polyangiitis under a new consensus algorithm of ANCA-associated vasculitides in Korea. Rheumatol Int 32(10):2979–2986
5. Mun CH, Yoo J, Jung SM, Song JJ, Park YB, Lee SW (2018) The initial predictors of death in 153 patients with ANCA-associated vasculitis in a single Korean centre. Clin Exp Rheumatol
6. Xu PC, Tong ZY, Chen T, Gao S, Hu SY, Yang XW, et al. (2018) Hypoalbuminaemia in antineutrophil cytoplasmic antibody-associated vasculitis: incidence and significance. Clin Exp Rheumatol
7. O'Connell TX, Horita TJ, Kasravi B (2005) Understanding and interpreting serum protein electrophoresis. Am Fam Physician 71(1):105–112
8. Du XJ, Tang LL, Mao YP, Sun Y, Zeng MS, Kang TB et al (2014) The pretreatment albumin to globulin ratio has predictive value for long-term mortality in nasopharyngeal carcinoma. PLoS One 9(4): e94473
9. Suh B, Park S, Shin DW, Yun JM, Keam B, Yang HK, Ahn E, Lee H, Park JH, Cho B (2014) Low albumin-to-globulin ratio associated with cancer incidence and mortality in generally healthy adults. Ann Oncol 25(11):2260–2266
10. Azab B, Bibawy J, Harris K, Khoueiry G, Akerman M, Selim J, Khalil S, Bloom S, McGinn JT Jr (2013) Value of albumin-globulin ratio as a predictor of all-cause mortality after non-ST elevation myocardial infarction. Angiology 64(2):137–145
11. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S et al (2011) Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 68(12): 1827–1832
12. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P, French Vasculitis Study Group (FVSG) (2011) The five-factor score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 90(1):19–27
13. Csernok E, Moosig F (2014) Current and emerging techniques for ANCA detection in vasculitis. Nat Rev Rheumatol 10(8):494–501
14. Murray CJ, Atkinson C, Bhalla K, Birbeck G, Burstein R, Chou D, Dellavalle R, Danaei G, Ezzati M, Fahimi A, Flaxman D, Foreman, Gabriel S, Gakidou E, Kassebaum N, Khatibzadeh S, Lim S, Lipshultz SE, London S, Lopez, MacIntyre M, Mokdad AH, Moran A, Moran AE, Mozaffarian D, Murphy T, Naghavi M, Pope C, Roberts T, Salomon J, Schwebel DC, Shahraz S, Sleet DA, Murray, Abraham J, Ali MK, Atkinson C, Bartels DH, Bhalla K, Birbeck G, Burstein R, Chen H, Criqui MH, Dahodwala, Jarlais, Ding EL, Dorsey ER, Ebel BE, Ezzati M, Fahami, Flaxman S, Flaxman AD, Gonzalez-Medina D, Grant B, Hagan H, Hoffman H, Kassebaum N, Khatibzadeh S, Leasher JL, Lin J, Lipshultz SE, Lozano R, Lu Y, Mallinger L, McDermott M, Micha R, Miller TR, Mokdad AA, Mokdad AH, Mozaffarian D, Naghavi M, Narayan KM, Omer SB, Pelizzari PM, Phillips D, Ranganathan D, Rivara FP, Roberts T, Sampson U, Sanman E, Sapkota A, Schwebel DC, Sharaz S, Shivakoti R, Singh GM, Singh D, Tavakkoli M, Towbin JA, Wilkinson JD, Zabetian A, Murray, Abraham J, Ali MK, Alvardo M, Atkinson C, Baddour LM, Benjamin EJ, Bhalla K, Birbeck G, Bolliger I, Burstein R, Carnahan E, Chou D, Chugh SS, Cohen A, Colson KE, Cooper LT, Couser W, Criqui MH, Dabhadkar KC, Dellavalle RP, Jarlais, Dicker D, Dorsey ER, Duber H, Ebel BE, Engell RE, Ezzati M, Felson DT, Finucane MM, Flaxman S, Flaxman AD, Fleming T, Foreman, Forouzanfar MH, Freedman G, Freeman MK, Gakidou E, Gillum RF, Gonzalez-Medina D, Gosselin R, Gutierrez HR, Hagan H, Havmoeller R, Hoffman H, Jacobsen KH, James SL, Jasrasaria R, Jayarman S, Johns N, Kassebaum N, Khatibzadeh S, Lan Q, Leasher JL, Lim S, Lipshultz SE, London S, Lopez, Lozano R, Lu Y, Mallinger L, Meltzer M, Mensah GA, Michaud C, Miller TR, Mock C, Moffitt TE, Mokdad AA, Mokdad AH, Moran A, Naghavi M, Narayan KM, Nelson RG, Olives C, Omer SB, Ortblad

K, Ostro B, Pelizzari PM, Phillips D, Raju M, Razavi H, Ritz B, Roberts T, Sacco RL, Salomon J, Sampson U, Schwebel DC, Shahraz S, Shibuya K, Silberberg D, Singh JA, Steenland K, Taylor JA, Thurston GD, Vavilala MS, Vos T, Wagner GR, Weinstock MA, Weisskopf MG, Wulf S, Murray, U.S. Burden of Disease Collaborators (2013) The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA 310(6):591–608

15. Koo BK, Lee CH, Yang BR, Hwang SS, Choi NK (2014) The incidence and prevalence of diabetes mellitus and related atherosclerotic complications in Korea: a National Health Insurance Database Study. PLoS One 9(10):e110650
16. Kim NH, Lee J, Kim TJ, Kim NH, Choi KM, Baik SH, Choi DS, Pop-Busui R, Park Y, Kim SG (2015) Body mass index and mortality in the general population and in subjects with chronic disease in Korea: a nationwide cohort study (2002-2010). PLoS One 10(10):e0139924