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ORIGINAL ARTICLE

The prognostic values of beta-2 microglobulin for risks of cardiovascular events and mortality in the elderly patients with isolated systolic hypertension

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Background: The present study aimed to investigate the effects of serum beta-2 microglobulin (B2M) on the risks of major cardiovascular events (MACEs) and all-cause death in Chinese elderly isolated systolic hypertension (ISH) patients without severe renal insufficiency (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2). **Materials and Methods:** Serum B2M concentration, creatinine-eGFR, and blood pressure variability were evaluated in 460 elderly patients (mean age, 82.6 years; 28 women) with ISH in this observational study. The Cox proportional hazard model was adopted to calculate adjusted hazard ratios (HRs) of risk factors for cardiovascular events and all-cause deaths. **Results:** During a median follow-up period of 37.6 months, 63 patients (13.7%) died, and 65 patients (14.1%) had MACEs. Multivariable analysis showed that the higher serum B2M concentration (B2M ≥0.28 mg/dl) was an independent predictor of increased risk of MACEs (nonfatal acute myocardial infarction, acute heart failure, ischemic stroke, and cardiovascular deaths) and all-cause death (HR: 2.62, 95% confidence interval [CI]: 1.46–4.69, P = 0.001 and HR: 3.40, 95% CI: 1.78–6.48, P < 0.001, respectively) adjusting for other multiple confounders including creatinine-eGFR and cystatin C. In addition, blood pressure variability derived from ambulatory blood pressure measurement was not associated with incidence of MACEs and all-cause mortality (P > 0.05). **Conclusion:** Our data suggest that serum B2M concentration may be individually associated with MACEs and all-cause death in elderly ISH patients without severe renal insufficiency even after adjusted for creatinine-eGFR and cystatin C.

Key words: Beta-2 microglobulin, cardiovascular event, elderly, isolated systolic hypertension, mortality

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INTRODUCTION

Isolated systolic hypertension (ISH) has been revealed as an independent risk factor for cardiovascular diseases such as left ventricular hypertrophy (LVH), heart failure, coronary heart disease, and stroke.[1,2] ISH could also cause renal damage in an early stage, and the renal damage often happens insidiously and persists for many years without any typical clinical manifestations. Therefore, how to detect early mild renal insufficiency is crucial. Some serum markers of renal function filtered by the renal glomerulus such as beta-2 microglobulin (B2M) and cystatin C are thought to be more sensitive parameters for renal function assessment and stronger predictors for death and cardiovascular events compared to serum creatinine (SCr).[3,4] B2M is a polypeptide which is present on the surface of nucleated human cells and thrombocytes.[5] It has been viewed as a useful parameter for estimated glomerular filtration rate (eGFR) and detecting mild-to-moderate renal insufficiency.[6] The serum B2M concentration in the elderly patients was found to be related to some nonrenal determinants such as systolic blood pressure (SBP), total cholesterol, smoking, glucocorticoid therapy, and inflammatory conditions except for renal determinants in recent studies.[7] The serum B2M concentration has been revealed as an independent predictor of total

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mortality in the general population or elderly patients, even when the eGFR was in normal range.[8] However, the prognostic value of serum B2M concentration for risks of cardiovascular events and all-cause death in elderly ISH patients without severe renal insufficiency in China has not been elucidated.

The aim of this observational study was to evaluate whether the elevated serum B2M was a predictor for major cardiovascular events (MACEs) and all-cause mortality in the elderly patients with ISH adjusting for other renal parameters such as creatinine-eGFR and cystatin C.

MATERIALS AND METHODS

Study population

According to the previous studies such as "Amighi *et al.* stroke, in 2011,"[9] the estimated incidence of MACEs in the elevated B2M group (B2M ≥0.28 mg/dl) was 17% whereas the estimated incidence of MACEs in the lower B2M group (B2M <0.28 mg/dl) was 7%. The sample size was calculated with PASS statistics version 11.0. Error rates were defined as follows: $\alpha = 0.05$; $\beta = 0.10$. The estimated sample size was 440. We reviewed the data of a total of 460 hospitalized elderly patients with ISH who were admitted because of hypertension in Chinese PLA General Hospital from January 2010 to June 2012. The hospital electronic medical database recorded all of the medical histories, therapeutic procedures, cardiovascular events, deaths, laboratory, and imaging data. The inclusion criteria included the following: (1) patients aged over 65 years; (2) established ISH. ISH was defined either by registration of the diagnosis in the previous medical chart, the use of antihypertensive medication or SBP ≥140 mmHg and diastolic blood pressure (DBP) <90 mmHg. We excluded patients with acute myocardial infarction (MI) and confirmed stroke within 6 months. Patients with secondary hypertension, critical aortic or mitral stenosis, malignant tumors, severe renal insufficiency (eGFR <30 ml/min/1.73 m^2), autoimmune nephrosis, nephrotic syndrome, glomerulonephritis, antiphospholipid syndrome, and uncontrolled infection were also excluded from the study.

Definitions

General health status, gender, body mass index (BMI), and personal histories of cardiovascular diseases were recorded on admission. Several echocardiography parameters such as the left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), and posterior wall thickness (PWT) were derived from the echocardiographic data. The left ventricular ejection fraction (LVEF) was measured using Simpson's method according to the recommendations of the American Society of Echocardiography. The left ventricular mass (LVM) was calculated according to the formula as follows: $0.8 \times (1.04 \times [\text{LVEDD} + \text{PWT} + \text{IVST}]^3 - \text{LVEDD}^3) + 0.6$ (g)[10] and indexed for body surface area as LVM index (LVMI). We defined left ventricular mass index greater than 125g/m^2 for men and greater than 110g/m^2 for women as the cut-off values of left ventricular hypertrophy (LVH).[11] Renal insufficiency was defined as creatinine-eGFR <60 ml/min/1.73 m^2, while severe renal insufficiency was defined as creatinine-eGFR<30ml/min/1.73m^2,[12] using the abbreviated equation as follows: $\text{EGFR} = 186 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742$ if female) $\times 1.233$, where SCr is serum creatinine and 1.233 is the adjustment coefficient for Chinese.[13]

Outcome ascertainment

The major study outcomes included MACEs as follows: nonfatal acute MI, acute heart failure, ischemic stroke and cardiovascular deaths. Cardiovascular deaths were attributed to MI, heart failure, and sudden cardiac death. Acute MI accorded with at least two criteria in coronary heart disease patients as follows: (1) typical chest pain, (2) typical electrocardiography evolution process of MI, (3) and dynamic change of typical myocardial markers. Acute heart failure was defined as a rapid onset or worsening of symptoms and/or signs of heart failure reflecting overload (pulmonary congestion and/or peripheral edema).[13] Ischemic stroke was defined as a sudden onset of neurological deficit lasting for >24 h, and was confirmed by computed tomography or magnetic resonance imaging according to the Oxford classification. Information of the end-points was collected from the medical records and electronic database.

Twenty-four-hour ambulatory blood pressure monitoring parameters and measurement of biomarkers

All the participants accepted ambulatory blood pressure monitoring (ABPM) on admission. ABPM was performed with a portable lightweight device (Mobil-O-Graph, I.E.M., Stolberg, Germany). We calculated the means of 24-h BP, daytime BP, and nighttime BP. Standard deviation (SD) as an index of BP variability was calculated separately for day and night, respectively.

Assessments of SCr, serum cystatin C (The previous studies had shown that serum cystatin C was almost the same sensitive parameter for renal function assessment compared with B2M especially in patients with mild to moderate renal insufficiency. Serum cystatin C was also associated with cardiovascular adverse events and death in patients with stroke, coronary heart disease and heart failure. Cystatin C was used to futher analyze the interaction between cystatin C and B2M), B2M, blood uric acid (BUA), and hemoglobin (Hb) were performed in the central laboratory of our hospital from blood samples obtained on admission.

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Statistical analyses

All statistical analyses were performed using IBM SPSS statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were shown as the mean ± SD. Univariate analysis was computed using the unpaired independent samples *t*-test for continuous variables and Chi-square test for categorical variables. Data with a nonnormal distribution were shown as median with interquartile range. The cumulative incidences of adverse events were plotted as the Kaplan–Meier curves between the different groups, and the differences were assessed using the log rank test. The Cox proportional hazard models were adopted to calculate the adjusted hazard ratio (HR) of risk factors for adverse events. Adjusted HRs with 95% confidence intervals (CIs) were reported separately.

RESULTS

The baseline characteristics

A total of 460 elderly patients with ISH (females, 6.1%; mean age at baseline, 82.58 ± 9.06 years) were followed up for a median of 3.25 years. All patients were divided into two groups according to the median of serum B2M concentration (0.28 mg/dl). Baseline characteristics of the study population are reported in Table 1. In this cohort, the patients in the elevated B2M group (B2M ≥0.28 mg/dl) had higher prevalences of coronary heart disease, heart failure, renal insufficiency, MI, hyperuricemia, prior hemorrhage, and anemia than those in the control group (B2M <0.28 mg/dl), respectively (all $P < 0.05$). No statistically significant differences were observed between the two groups in gender, BMI, follow-up period, prior stroke, diabetes mellitus (DM), peripheral arterial disease (PAD), and atrial fibrillation (AF). Student's *t*-test showed that values of age, cystatin C, SCr, and BUA were significantly higher in the elevated B2M category group compared to those in the control group. The lower B2M category was associated with higher total DBP, higher SD of nighttime DBP, higher daytime/nighttime DBP, higher LVEF, higher eGFR, and higher Hb (all $P < 0.05$). There were no significant differences in total SBP, SD of daytime SBP, SD of daytime DBP, SD of nighttime SBP, daytime SBP, and nighttime SBP between the two groups. The patients with elevated serum B2M concentration were treated more frequently with oral diuretics than patients in the control group ($P < 0.05$) [Table 2].

Table 1: Baseline characteristics of the study participants according to serum beta-2 microglobulin concentration

Variables	Overall (*n*=460)	B2M <0.28 mg/dl (*n*=230)	B2M ≥0.28 mg/dl (*n*=230)	*P*
Demographic profile				
Age (year)	82.58±9.06	78.48±9.72	86.68±6.02	<0.001
Gender (females), *n* (%)	28 (6.1)	13 (5.7)	15 (6.5)	0.697
BMI (kg/m^2)	24.68±3.21	24.68±2.96	24.68±3.44	0.997
Follow-up (month)	37.59±12.68	38.32±12.54	36.83±12.71	0.208
Morbidity profile, *n* (%)				
Coronary heart disease	324 (70.4)	140 (60.9)	184 (80.0)	<0.001
HF	51 (11.1)	13 (5.7)	38 (16.5)	<0.001
Prior stroke	71 (15.4)	31 (13.5)	40 (17.4)	0.245
Diabetes mellitus	157 (34.1)	70 (30.4)	87 (37.8)	0.095
Myocardial infarction	59 (12.8)	20 (8.7)	39 (17.0)	0.008
Renal insufficiency	66 (14.4)	9 (3.9)	57 (24.8)	<0.001
PAD	79 (17.2)	33 (14.4)	46 (20.0)	0.108
AF	90 (19.6)	37 (16.1)	53 (23.0)	0.060
Prior hemorrhage	36 (7.8)	12 (5.2)	24 (10.4)	0.037
Anemia	47 (10.2)	11 (4.8)	36 (15.7)	<0.001
Echocardiographic parameters				
LVEF (%)	61.24±4.50	62.27±3.75	60.20±4.95	<0.001
LVMI (g/m^2)	119.38±91.40	113.88±19.93	124.89±127.62	0.197
LVH, *n* (%)	124 (27.0)	54 (23.5)	70 (30.4)	0.093
Laboratory findings				
B2M (mg/dl)	0.34±0.22	0.22±0.04	0.47±0.26	<0.001
Cystatin C (mg/dl)	0.12±0.09	0.09±0.02	0.15±0.11	<0.001
SCr (μmol/L)	90.90±37.29	77.78±16.45	104.01±46.60	<0.001
eGFR (ml/min/1.73 m^2)	82.36±28.73	92.94±25.01	71.79±28.35	<0.001
BUA (μmol/L)	351.64±98.54	328.54±89.14	374.74±102.20	<0.001
Hemoglobin (g/dl)	12.96±1.66	13.53±1.48	12.39±1.64	<0.001

Data are presented as mean±SD or *n* (%). BMI=Body mass index; PAD=Peripheral arterial disease; LVEF=Left ventricular ejection fraction; LVMI=Left ventricular mass index; LVH=Left ventricular hypertrophy; SCr=Serum creatinine; eGFR=Estimate glomerular filtration rate; BUA=Blood uric acid; B2M=Beta-2 microglobulin; HF=Heart failure; AF=Atrial fibrillation

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Clinical outcomes

Clinical outcomes and crude incidence rates of elderly patients with ISH according to serum B2M concentration are listed in Table 3. During the median of 3.25 years' follow-up, 63 patients (13.7%) died, and 65 patients (14.1%) had MACEs (19 patients had nonfatal acute MI, 10 patients had acute heart failure, 29 patients had ischemic stroke, and 17 patients died of cardiovascular deaths). The annual all-cause mortality in patients with higher B2M category was approximately 22.2% and declined to 5.2% in patients

Table 2: Comparisons of ambulatory blood pressure parameters and clinical medications

Variables	Overall (*n*=460)	B2M <0.28 mg/dl (*n*=230)	B2M ≥0.28 mg/dl (*n*=230)	*P*
BP - specific profile (mmHg)				
Total SBP	122.63±12.41	121.93±11.97	123.33±12.82	0.229
Total DBP	68.50±8.15	69.99±8.31	67.02±7.72	<0.001
SD of daytime SBP	13.66±4.56	13.57±4.91	13.74±4.19	0.689
SD of daytime DBP	9.04±2.62	9.16±2.76	8.91±2.48	0.314
SD of nighttime SBP	11.27±7.18	11.47±4.75	11.08±9.00	0.563
SD of nighttime DBP	8.88±4.27	9.32±3.42	8.42±4.94	0.025
Daytime SBP	123.03±13.07	122.67±12.44	123.40±13.69	0.550
Daytime DBP	69.00±8.56	70.60±8.63	67.40±8.19	<0.001
Nighttime SBP	123.05±16.56	121.70±14.14	124.40±18.60	0.080
Nighttime DBP	68.16±10.17	69.40±9.07	66.92±11.04	0.009
Procedure profile, *n* (%)				
CCB	259 (56.3)	126 (54.8)	133 (57.8)	0.511
ACEI or ARB	264 (57.4)	129 (56.1)	135 (58.7)	0.572
Beta - blocker	247 (53.7)	121 (52.6)	126 (54.8)	0.640
Diuretic	81 (17.6)	24 (10.4)	57 (24.8)	<0.001
Statin	297 (64.6)	148 (64.4)	149 (64.8)	0.973
Antiplatelet drug	325 (70.7)	160 (69.6)	165 (71.7)	0.609

Data are presented as mean±SD or *n* (%).BP=Blood pressure; SBP=Systolic BP; DBP=Diastolic BP; CCB=Calcium channel blocker; ACEI=Angiotensin-converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; SD=Standard deviation; B2M=Beta-2 microglobulin

Table 3: Incidences of adverse events according to the category of serum beta-2 microglobulin concentration

Adverse events	Overall		B2M <0.28 mg/dl		B2M ≥0.28 mg/dl		*P*
	Number of events, *n* (%)	Incidence rate, (%/year)	Number of events, *n* (%)	Incidence rate, (%/year)	Number of events, *n* (%)	Incidence rate, (%/year)	
MACEs	65 (14.1)	4.51	16 (7.0)	2.18	49 (21.3)	6.94	<0.001
Cardiac death	17 (3.7)	1.18	3 (1.3)	0.41	14 (6.1)	1.98	0.007
Ischemic stroke	29 (6.3)	2.01	11 (4.8)	1.50	18 (7.8)	2.55	0.179
Acute MI	19 (4.1)	1.32	4 (1.7)	0.54	15 (6.5)	2.12	0.010
Acute HF	10 (2.2)	0.69	1 (0.4)	0.14	9 (3.9)	1.27	0.011
All-cause death	63 (13.7)	4.37	12 (5.2)	1.63	51 (22.2)	7.22	<0.001
Major bleeding	22 (4.8)	1.53	4 (1.7)	0.54	18 (7.8)	2.55	0.002

Data are presented as *n* (%) unless otherwise stated. MACEs=Major cardiovascular events; B2M=Beta-2 microglobulin; MI=Myocardial infarction; HF=Heart failure

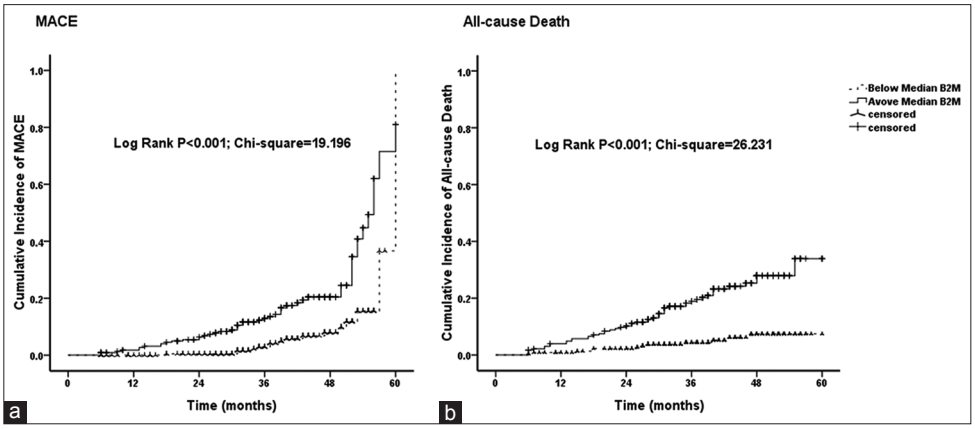

Figure 1: Kaplan–Meier estimates of cumulative incidences of (a) major cardiovascular events and (b) all-cause death according to the categories of beta-2 microglobulin

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with lower B2M category ($P < 0.01$). The annual rate of MACEs was 21.3% in patients with higher B2M category and was 7.0% in patients with lower B2M category. On univariate analysis, the Kapan–Meier estimates of cumulative incidences of MACEs and all-cause mortality increased with the B2M categories, respectively (all $P < 0.05$) [Figure 1].

Multivariable analyses

Univariate and multivariable Cox regression analyses of risk factors for MACEs and all-cause death are shown in Table 4. Model 1 was a univariate model. Multivariable Cox regression model 2 was applied including creatinine-eGFR and other basic risk factors such as age, gender, LVH, BMI, coronary heart disease, heart failure, prior stroke, intracranial hemorrhage, DM, prior MI, PAD, AF, hyperuricemia, prior bleeding, anemia, and pressure parameters. Multivariable Cox regression model 3 was further adjusted for B2M and cystatin C on the base of model 2. At the end of the follow-up, the crude HRs for MACEs and all-cause death in the patients with elevated B2M category were higher than those with lower B2M category, and remained statistically significant (HR: 2.62, 95% CI: 1.46–4.69, $P = 0.001$ and HR: 3.40, 95% CI: 1.78–6.48, $P < 0.001$, respectively) after adjusting for other multiple confounders including creatinine-eGFR and cystatin C.

In addition, after adjusting for other risk factors, MI, heart failure, and anemia were independent risk factors for MACEs (HR: 2.103, 95%CI: 1.13–3.90; HR: 2.87, 95%CI: 1.41–5.87 and HR: 2.50, 95% CI: 1.27–4.91, respectively). LVH, heart failure, and anemia were independent risk factors for all-cause death (HR: 1.93, 95% CI: 1.16–3.21; HR: 2.84, 95% CI: 1.51–5.31 and HR: 2.53, 95% CI: 1.39–4.59, respectively). In addition, we found no association between measures of BP variability and clinical outcomes such as MACEs and all-cause death.

DISCUSSION

ISH is a distinct type of hypertension characterized by elevated SBP without elevation of DBP. The mechanism of ISH has proposed to be related to the increased stiffness of the large arteries and reflected waves from peripheral vessels.[14] ISH has been revealed to cause renal damage in an early stage. As a useful parameter for detecting mild renal insufficiency, B2M might be a more accurate predictor of cardiovascular disease prognosis than other filtration markers. The present study demonstrated that a higher

Table 4: Univariate and multivariable Cox regression analyses of risk factors for major cardiovascular events, all-cause death, and major bleeding events

Adverse events	Model 1			Model 2			Model 3		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
MACEs									
LVH*	2.148	1.286-3.590	0.004	1.852	1.092-3.141	0.022			
Beta blocker	1.748	1.051-2.907	0.032						
Myocardial infarction	2.925	1.646-5.199	<0.001	2.010	1.070-3.778	0.030	2.103	1.134-3.899	0.018
HF	4.526	2.329-8.797	<0.001	3.204	1.552-6.615	0.002	2.873	1.408-5.865	0.004
eGFR <60 ml/min/1.73 m^2	2.220	1.317-3.741	0.003						
Anemia	3.289	1.695-6.382	<0.001	3.009	1.530-5.921	0.001	2.497	1.269-4.914	0.008
B2M ≥0.28 mg/dl	3.258	1.850-5.737	<0.001				2.619	1.462-4.690	0.001
Cystatin C >0.1 mg/dl	2.618	1.499-4.572	0.001						
All-cause death									
LVH*	2.371	1.441-3.902	0.001	2.022	1.214-3.370	0.007	1.930	1.161-3.209	0.011
HF	4.179	2.265-7.709	<0.001	3.682	1.975-6.863	<0.001	2.835	1.513-5.313	0.001
Anemia	3.601	2.011-6.448	<0.001	3.222	1.780-5.833	<0.001	2.526	1.390-4.590	0.002
eGFR <60 ml/min/1.73 m^2	2.543	1.514-4.270	<0.001						
B2M ≥0.28 mg/dl	4.467	2.381-8.379	<0.001				3.395	1.779-6.477	<0.001
Cystatin C >0.1 mg/dl	3.136	1.856-5.298	<0.001						
Major bleeding									
Anemia	5.338	2.048-13.913	0.001	5.555	2.116-14.581	<0.001	4.140	1.556-11.016	0.004
HF	4.126	1.383-12.313	0.011	4.364	1.452-13.117	0.009	3.338	1.094-10.181	0.034
eGFR <60 ml/min/1.73 m^2	3.280	1.399-7.690	0.006						
B2M ≥0.28 mg/dl	4.674	1.578-13.847	0.005				3.457	1.132-10.555	0.029
Cystatin C >0.1 mg/dl	2.022	0.816-5.009	0.128						

*LVH was defined as LVMI >125 g/m^2 for men and 110 g/m^2 for women. B2M=Beta-2 microglobulin; MACEs=Nonfatal acute myocardial infarction, heart failure, stroke and cardiovascular death; LVH=Left ventricular hypertrophy; eGFR=Estimate glomerular filtration rate; Model 1=Univariate model; Model 2=Adjusted for eGFR, age, gender, LVH, BMI, coronary heart disease, HF, prior stroke, intracranial hemorrhage, diabetes mellitus, prior myocardial infarction, peripheral arterial disease, atrial fibrillation, prior bleeding and anemia; Model 3=Further adjusted for B2M and cystatin C based on Model 2; HF=Heart failure; CI=Confidence interval; HR=Hazard ratio; LVMI=Left ventricular mass index

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category of serum B2M concentration (B2M ≥0.28 mg/dl) was individually associated with increased risks of MACEs and all-cause death after adjustment for other traditional risk factors including creatinine-eGFR and cystatin C in elderly ISH patients without eGFR<30ml/min/1.73m^2. In addition, we found no association between measures of BP variability and clinical outcomes such as MACEs and all-cause death.

The previous studies had demonstrated that the prevalence of ISH was approximately 5.1%–11.9%, among the adult population in China, and increased with age for both men and women.[1] Although it was the most important goal in the elderly patients with ISH to decrease the BP to the recommended targets, the treatment of cardiovascular risk factors and subclinical target-organ damages were essential. Renal insufficiency was one of the most common complications in elderly patients with ISH, even in the early stage without any typical clinical manifestations. Plasma B2M is a low-molecular-weight protein freely filtered by the glomeruli and reabsorbed by the proximal tubular cells. The serum B2M concentration, which was primarily determined by eGFR, increased with several malignancies and infectious diseases, and decreased with the lipo-prostaglandin E1 intervention regardless of the degree of renal dysfunction.[15,16] Some studies demonstrated that the serum B2M concentration was associated with several nonrenal factors such as blood pressure, gender, chronic inflammatory disease, and age.[7,9] A higher serum concentration can be used as a highly sensitive marker for detecting kidney dysfunction.[16] More importantly, higher B2M concentration was associated with or more strongly associated with death, cardiovascular event, incident cardiovascular disease (coronary disease, stroke, and heart failure),[17] and the prognosis in kidney disease independently,[8,18] even after adjustment for other factors such as eGFR, C-reactive protein, and history of heart disease or cancer.[5,19,20] Previous studies also found that the serum B2M concentration was associated with all-cause death in patients with uremia,[21] acute heart failure,[22] DM, acute coronary syndrome,[23] and asymptomatic carotid atherosclerosis.[8,9] The PROSPECT study even found that B2M strongly predicted MACEs within 3 years after percutaneous coronary intervention in acute coronary syndrome.[23] The favorite trial also found B2M was strongly associated with cardiovascular events and mortality in stable kidney transplant recipients.[24] However, related data on elderly patients with ISH are scarce at present. In this study, we confirmed the elevated serum B2M concentration increased with the kidney function parameters such as SCr, serum BUN, and serum cystatin C. Similarly, in NHANES III and some other studies,[25] several nonkidney factors were also associated with elevated serum B2M concentration including older age and lower Hb. Moreover, our present data suggested higher serum B2M concentration was an independent risk factor for MACEs and all-cause death in elderly ISH patients without severe renal insufficiency. However, the mechanisms by which B2M increased mortality risk were not well understood. The potential causes might include the following: (1) serum B2M concentration was a highly sensitive marker for kidney insufficiency after adjustment for eGFR and strongly associated with prognosis in kidney disease;[8] (2) the high serum B2M concentration might damage vessels by participating in amyloid formation in the vascular wall;[5] (3) serum B2M concentration was a marker of chronic inflammation; (4) and there was a correlation between serum B2M concentration and arterial stiffness associated with heart failure and atrial arrhythmia.[26,27] In addition, we found that the serum B2M concentration had a superior value to distinguish the risk of MACEs and all-cause death compared to baseline serum cystatin C and eGFR. This finding was consisting of the previous study that found the serum B2M was more sensitive than creatinine in predicting cardiovascular events in patients with chronic kidney disease.[28] It suggested serum B2M level may contribute additional risk information beyond eGFR among persons with moderate chronic kidney disease and was an important link between the kidney and the cardiovascular diseases.[29]

In this study, another finding was that there was no association between measures of BP variability derived from ambulatory BP measurement and clinical outcomes. The result was similar to those studies which showed BP variability could not predict the risk of cardiovascular events beyond the BP level.[30] However, the BP variability derived from ambulatory BP measurement (short-term BP variability) may have insufficient statistical power to clarify the correlation compared to the visit-to-visit BP variability.

Limitations

This study has several limitations. First, our data came from in-hospital patients and based on the relatively small sample size, which could induce patient selection bias. Second, in our cohort, only 6.1% of patients were female, which could affect the sex-specific risk of adverse events. Third, it was not taken into account that changes in serum B2M concentrations might have occurred during the follow-up period. Finally, we excluded elderly ISH patients with severe renal insufficiency (eGFR<30ml/min/1.73m^2); hence, the present results may not be generalizable to all elderly ISH patients. A larger sample prospective and long-term follow-up study should be further investigated.

CONCLUSION

The serum B2M concentration was individually associated with MACEs (nonfatal acute MI, acute heart failure, ischemic

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stroke, and cardiovascular deaths) and all-cause death in elderly ISH patients without eGFR<30ml/min/1.73m^2 even adjusted for creatinine-eGFR and cystatin C. No correlation was found between blood pressure variability and the incidence of MACEs or all-cause mortality.

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Conflicts of interest

There are no conflicts of interest.

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