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Factors Influencing Aspirin Hyporesponsiveness in Elderly Chinese Patients

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Background: Aspirin hyporesponsiveness increases the risk of ischemic events. Therefore, it is important to investigate the factors influencing aspirin hyporesponsiveness.

Material/Methods: Patients aged 60 years or older who did not take aspirin before enrollment were included, with aspirin 100 mg/day administered after enrollment. The arachidonic acid-induced platelet aggregation rate (Ara) was measured by light transmission assay to evaluate aspirin responsiveness. Patients with Ara in the upper quartile after taking aspirin were assigned to the aspirin hyporesponsive group (Ara-Q4).

Results: A total of 292 elderly patients were included. The median value of Ara after taking aspirin was 5.87% (interquartile range 3.86-10.04%). Compared with the aspirin non-hyporesponsive group (Ara-Q1-3, Ara ≤10.04%, n=220), the level of uric acid (UA) (341.30 μmol/L *vs.* 299.10 μmol/L, p=0.027) and the ratios of β-blockers (9.72% *vs.* 2.27%, p=0.015) and diuretics (6.94% *vs.* 1.36%, p=0.036) were higher in the aspirin hyporesponsive group (Ara-Q4, Ara >10.04%, n=72). After multivariate adjustment, the results demonstrated baseline Ara (odds ratio [OR]: 1.030, 95% confidence interval [CI]: 1.004–1.056, p=0.021), UA level (OR: 1.003, 95% CI: 1.000–1.006, p=0.038), and β-blockers use (OR: 5.487, 95% CI: 1.515–19.870, p=0.010) were independently and positively associated with aspirin hyporesponsiveness.

Conclusions: This study found that baseline Ara, UA level, and β-blockers use were independently and positively associated with aspirin hyporesponsiveness in elderly Chinese patients, which needs to be validated in large-scale studies.

MeSH Keywords: Aspirin • Frail Elderly • Platelet Aggregation Inhibitors

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/917654

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Background

With the rapid increase of the elderly population, cardiovascular diseases have become the primary threat to human life and health. Studies have well documented that aspirin can significantly reduce major adverse cardiovascular events (MACE) through irreversible inhibition of platelet aggregation [1,2]. However, there are still numerous patients suffering from MACE despite being on regular aspirin therapy [3,4], which is associated with aspirin hyporesponsiveness.

Aspirin hyporesponsiveness, also called high on-aspirin platelet reactivity, is defined as incomplete inhibition of platelet aggregation after taking aspirin. To date, there is still no consensus on the cut-off value of aspirin hyporesponsiveness [4–7]. Studies have demonstrated that aspirin hyporesponsiveness increases the risk of ischemic events [8,9]. Therefore, it is of great significance to investigate the factors influencing aspirin hyporesponsiveness, which could help to identify patients at a high risk of ischemic events. However, relevant data on elderly patients are scarce, particularly in China. Consequently, this study investigated potential factors influencing aspirin hyporesponsiveness in elderly Chinese patients.

Material and Methods

Patient selection

From September 2016 to December 2016, patients aged 60 years or older from 18 hospitals in China who did not take aspirin before enrollment were included (No. ChiCTR1800018517). The inclusion criteria were: (1) age 60 years or older; (2) regularly took aspirin 100 mg/day at least 7 days after enrollment; (3) patients who took aspirin for primary prevention had to have 1) at least 1 of these 3 diseases: hypertension, diabetes mellitus (DM), and dyslipidemia; or 2) at least 2 of the following conditions: smoking, body mass index (BMI) ≥28.00 kg/m^2, and family history of premature cardiovascular diseases (men <55 years, women <65 years); (4) patients who took aspirin for secondary prevention had to have at least 1 of the following diseases: 1) stable clinically diagnosed-coronary heart diseases; and 2) stable stent-implantation in coronary artery for more than 1 year with aspirin monotherapy.

The exclusion criteria were: (1) allergy or contraindication of aspirin; (2) at a high risk of bleeding, such as erosive gastritis, peptic ulcer, history of gastrointestinal or intracranial hemorrhage; (3) platelet count <80×10^9/L or >500×10^9/L; (4) concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), other antiplatelet medications, glycoprotein IIβ/IIIα receptor inhibitors, vitamin K antagonists, or novel anticoagulants; (5) left main coronary artery diseases or severe 3-vessel diseases; and (6) other unsuitable patients such as those with malignant tumor, severe liver dysfunction, or severe renal dysfunction.

The study was carried out in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Review Committee of Peking University First Hospital (No. 2016[1175]). Written informed consent was obtained from all participants.

Medical records collection

For each patient, detailed medical records on enrollment were collected, including demographic information, comorbidities, concomitant medications, and baseline biological parameters.

Light transmission assay

To evaluate aspirin responsiveness (before and after taking aspirin), 0.50 mg/mL arachidonic acid-induced platelet aggregation rate (Ara) was measured by light transmission assay (LTA) using LBY-NJ4 platelet aggregometer (PRECIL, Beijing, China), as described previously [5].

Patient group

Patients with Ara in the upper quartile after taking aspirin (Ara-Q4) were defined as the aspirin hyporesponsive group, whereas patients with Ara below the upper quartile after taking aspirin (Ara-Q1-3) were defined as the aspirin non-hyporesponsive group [5].

Subgroup studies were conducted by age (≥80 years or not), bodyweight (≥70 kg or not), BMI (≥28.00 kg/m^2 or not), and smoking amount (≥20 pack-years or not).

The cut-off value of hyperuricemia in the elderly was defined as uric acid (UA) concentration >416.50 μmol/L (7 mg/dL) in men and >357.00 μmol/L (6 mg/dL) in women [10].

Statistical analysis

Conformity to normal distribution was evaluated for continuous variables using the Kolmogorov-Smirnov test. Continuous variables were described as mean ±SD or median (interquartile range, IQR), whereas categorical variables were described as frequency (percent). The independent *t* test or nonparametric Mann-Whitney U test was used to compare continuous variables, whereas chi-square or Fisher exact test was applied for categorical variables. Spearman's correlation analysis was used to assess the correlation between influencing factors and aspirin hyporesponsiveness. Binary logistic regression analysis was performed to adjust multivariate factors of aspirin hyporesponsiveness. Receiver operating characteristic curve (ROC) analysis was used to evaluate the predictive value of potential

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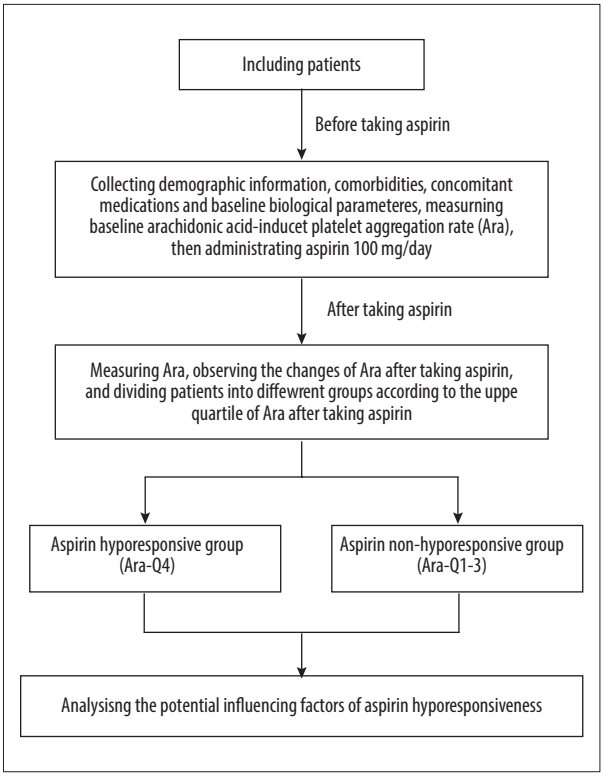

Figure 1. The flowchart of the study. Ara – arachidonic acid-induced platelet aggregation rate.

influencing factors. A 2-tailed p-value < 0.05 was statistically significant. Statistical analysis was carried out using SPSS version 22.0 software (SPSS, Inc., Chicago, IL, USA). The flowchart of the study is shown in Figure 1.

Results

Enrollment

A total of 292 elderly patients (age range 60–88 years) were included. The average age was 66.51±6.05 years, and 116 (39.73%) patients were males. There were 13 (4.45%) patients with age ≥80 years, 111 (38.01%) patients with bodyweight ≥70 kg, and 31 (10.62%) patients with BMI ≥28.00 kg/m^2. Among the 50 (17.12%) smoking patients, 34 (68.00%) smoked ≥20 pack-years. Comorbidities and concomitant medications are shown in Table 1.

Distribution of platelet aggregation rate

The range of baseline Ara was from 44.94% to 100.00%, with a median value of 82.62% (IQR 72.55%-89.28%). The range of decrease in Ara after taking aspirin was from 30.06% to 97.24%, with a median value of 74.18% (IQR 64.44–81.68%). The range of Ara after taking aspirin was from 1.01% to 43.51%, with a median value of 5.87% (IQR 3.86–10.04%).

Table 1. Clinical data of all patients.

	Patients (n=292)	
Age, years	66.51±6.05	
60–79 years, n (%)	279	(95.55)
≥80 years, n (%)	13	(4.45)
Sex		
Male, n (%)	116	(39.73)
Female, n (%)	176	(60.27)
Body weight		
<70 kg, n (%)	181	(61.99)
≥70 kg, n (%)	111	(38.01)
BMI		
<28.00 kg/m^2, n (%)	261	(89.38)
≥28.00 kg/m^2, n (%)	31	(10.62)
Smoking amount (n=145)		
<20 pack-years, n (%)	16	(32.00)
≥20 pack-years, n (%)	34	(68.00)
Comorbidities		
Hypertension, n (%)	201	(68.84)
DM, n (%)	65	(22.26)
Dyslipidemia, n (%)	146	(50.00)
CHD, n (%)	20	(6.85)
PCI, n (%)	4	(1.37)
Concomitant medications		
Statins, n (%)	32	(10.96)
ACEI, n (%)	20	(6.85)
ARB, n (%)	32	(10.96)
β-blockers, n (%)	12	(4.11)
CCB, n (%)	94	(32.19)
Diuretics, n (%)	8	(2.74)
Nitrates, n (%)	2	(0.68)
Hypoglycemics, n (%)	38	(13.01)
PPI, n (%)	1	(0.34)

BMI – body mass index; DM – diabetes mellitus; CHD – coronary heart diseases; PCI – percutaneous coronary intervention; ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CCB – calcium channel blockers; PPI – proton pump inhibitors.

Spearman's correlation analysis showed the extent of decrease in Ara after taking aspirin was positively correlated with age

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Table 2. The correlation between the decreasing extent of Ara after taking aspirin and potential influencing factors.

			Age	Body weight	BMI	Smoking amount
Spearman's rho	The decreasing extent of Ara	Correlation Coefficient	0.145	–0.079	–0.017	0.127
		P-value	0.013*	0.177	0.774	0.379
		N	292	292	292	50

Ara – arachidonic acid-induced platelet aggregation rate; BMI – body mass index.

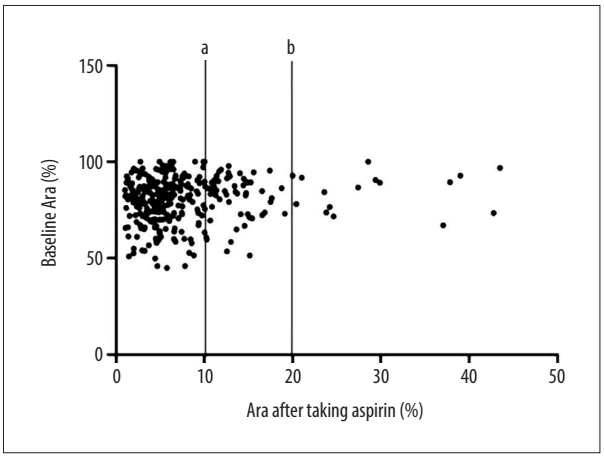

Figure 2. The distribution of arachidonic acid-induced platelet aggregation rate (Ara). a: Ara=10.04% (Ara-Q4, Ara >10.04%, n=72), b: Ara=20% (Ara >20%, n = 15)

(r=0.145, p=0.013). There were no significant correlations between the extent of decrease in Ara after taking aspirin and bodyweight (r=–0.079, p=0.177), BMI (r=–0.017, p=0.774), or smoking amount (r=0.127, p=0.379), as shown in Table 2.

There were 15 (5.14%) patients with Ara >20%. According to the aforementioned definition, there were 72 patients in the aspirin hyporesponsive group (Ara-Q4, Ara >10.04%), with a median value of 14.28% (IQR 11.63%-18.49%), and there were 220 patients in the aspirin non-hyporesponsive group (Ara-Q1-3, Ara ≤10.04%), with a median value of 4.85% (IQR 3.26–6.56%). The distribution of Ara is shown in Figure 2.

Clinical features of aspirin hyporesponsive group

We compared patients' demographics, comorbidities, biological parameters, and concomitant medications between the aspirin hyporesponsive group (Ara-Q4) and the aspirin non-hyporesponsive group (Ara-Q1-3), as shown in Table 3. Compared with the aspirin non-hyporesponsive group (Ara-Q1-3), the level of UA (341.30 μmol/L *vs.* 299.10 μmol/L, p=0.027), and the ratios of β-blockers use (9.72% *vs.* 2.27%, p=0.015) and diuretics use (6.94% *vs.* 1.36%, p=0.036) were higher in the aspirin hyporesponsive group (Ara-Q4).

There were no significant differences in age ≥80 years (4/72, 5.56% *vs.* 9/220, 4.09%, p=0.846), bodyweight ≥70 kg (32/72, 44.44% *vs.* 79/220, 35.91%, p=0.195), BMI ≥28 kg/m^2 (11/72, 15.28% *vs.* 20/220, 9.09%, p=0.139), and smoking amount ≥20 pack-years (11/13, 84.62% *vs.* 23/37, 62.16%, p=0.251) between the aspirin hyporesponsive group (Ara-Q4) and the aspirin non-hyporesponsive group (Ara-Q1-3), as shown in Figure 3.

Compared with the aspirin non-hyporesponsive group (Ara-Q1-3), the incidence of hyperuricemia was higher in the aspirin hyporesponsive group (Ara-Q4) (23/69, 33.33% *vs.* 43/212, 20.28%, p=0.026), as shown in Figure 4.

Factors influencing aspirin hyporesponsiveness

Spearman's correlation analysis was performed to evaluate the correlation between aspirin hyporesponsiveness and those variables with a p-value <0.05 in Table 3 (UA, β-blockers, and diuretics). The results showed that the level of UA (r=0.132, p=0.027), use of β-blockers (r=0.162, p=0.006), and use of diuretics (r=0.147, p=0.012) were positively correlated with aspirin hyporesponsiveness (Table 4).

Binary logistic regression analysis was performed for multivariate adjustment. Age, sex, and variables listed in Table 3 with a p-value <0.10 (baseline Ara, triglyceride, UA, statins, β-blockers, diuretics) were selected. The results revealed that baseline Ara (odds ratio [OR]: 1.030, 95% CI: 1.004–1.056, p=0.021), UA level (OR: 1.003, 95% CI: 1.000–1.006, p=0.038) and β-blockers use (OR: 5.487, 95% CI: 1.515–19.870, p=0.010) were independently and positively associated with aspirin hyporesponsiveness (Table 5).

Receiver operating characteristic (ROC) curve analysis were used to assess the predictive value of variables with a p-value <0.05 in Table 5 (baseline Ara, UA, and β-blockers). The results showed that the area under the curve (AUC) of the UA level was 0.588 (95% CI: 0.508–0.669, p=0.027), as shown in Table 6.

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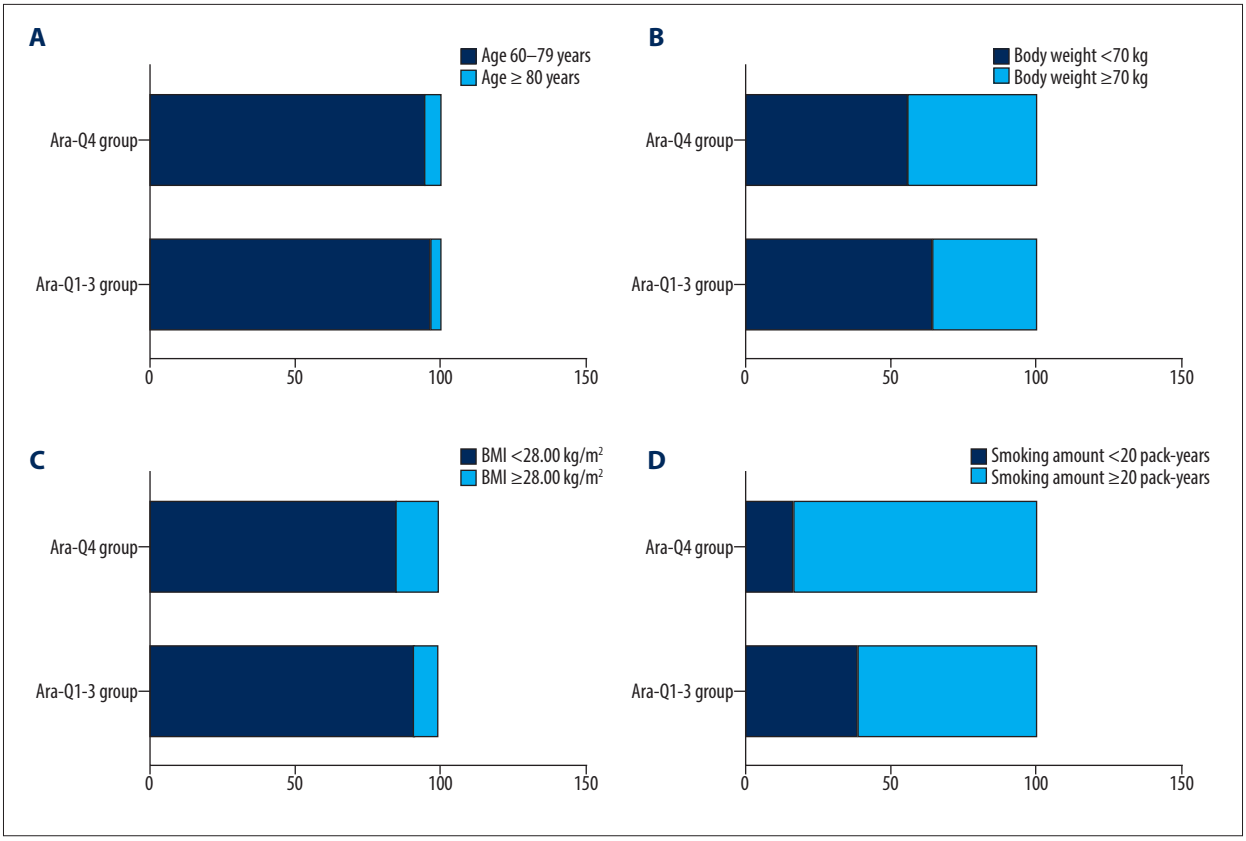

Figure 3. The composition proportions of (**A**) age, (**B**) bodyweight, (**C**) BMI, and (**D**) smoking amount in aspirin hyporesponsive group (Ara-Q4, n=72) and aspirin non-hyporesponsive group (Ara-Q1-3, n=220). BMI – body mass index; Ara – arachidonic acid-induced platelet aggregation rate.

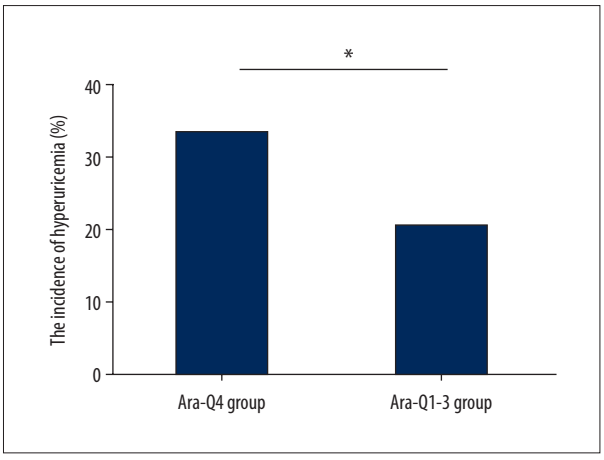

Figure 4. The incidence of hyperuricemia in aspirin hyporesponsive group (Ara-Q4, n=72) and aspirin non-hyporesponsive group (Ara-Q1-3, n=220). * p<0.05. Ara – arachidonic acid-induced platelet aggregation rate.

Discussion

To date, there is still no consensus on the definition of aspirin hyporesponsiveness, mainly because various methods are used to evaluate aspirin responsiveness, and there is no universally accepted cut-off value of each method used to define aspirin hyporesponsiveness [5,11,12]. In this study, LTA was used to assess aspirin responsiveness and Ara located in the upper quartile after taking aspirin (Ara-Q4) were defined as aspirin hyporesponsiveness [5].

Aspirin hyporesponsiveness increases the risk of ischemic events [13, 14]. Therefore, it is importance to investigate the factors influencing aspirin hyporesponsiveness. Dillinger et al. demonstrated DM and age were predictors of aspirin hyporesponsiveness [15]. Wang et al. found hypertension and DM were relative risk factors of aspirin hyporesponsiveness [16]. Both Capone et al. and Catella-Lawson et al. reported that concomitant administration of NSAIDs interfered with the inhibitory effect of aspirin [17,18]. However, relevant data in the elderly population are scant. The present study investigated the factors influencing aspirin hyporesponsiveness in elderly Chinese patients.

Advanced age is associated with high risk of ischemic events, which might be partly due to an increased incidence of aspirin hyporesponsiveness in this population [15,19]. In our study, a

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Table 3. Clinical features of different aspirin responsiveness groups.

	Aspirin hyporesponsive group (Ara-Q4, n=72)		Aspirin non-hyporesponsive group (Ara-Q1-3, n=220)		P-value
Patients' demographics					
Age (years)	64	(62–67)	66	(62–70)	0.139
Male, n (%)	32	(44.44)	84	(38.18)	0.346
Bodyweight (kg)	68	(60–74)	65	(60–71)	0.239
BMI (kg/m^2)	24.22	(22.46–26.34)	24.05	(22.86–26.02)	0.747
Smoking, n (%)	13	(18.06)	37	(16.82)	0.809
Drinking, n (%)	18	(25.00)	42	(19.09)	0.281
Comorbidities					
Hypertension, n (%)	53	(73.61)	148	(67.27)	0.313
DM, n (%)	17	(23.61)	48	(21.82)	0.751
Dyslipidemia, n (%)	37	(51.39)	109	(49.55)	0.786
CHD, n (%)	6	(8.33)	14	(6.36)	0.760
PCI, n (%)	1	(1.39)	3	(1.36)	> 0.999
Biological parameters					
Baseline Ara (%)	84.67	(73.67–90.44)	81.47	(71.76–88.63)	0.095#
WBC (×10^9/L)	5.77	(4.92–6.77)	5.92	(4.93–6.76)	0.506
RBC (×10^{12}/L)	4.63±0.48		4.63±0.45		0.973
Hb (g/L)	139.78±15.13		140.25±13.29		0.803
PLT (×10^9/L)	221.13±52.74		213.84±51.03		0.298
MPV (fl)	9.98±1.29		9.90±1.31		0.655
ALT > 40 IU/L, n (%)	2	(2.78)	17	(7.73)	0.238
AST > 40 IU/L, n (%)	1	(1.39)	8	(3.64)	0.568
TG (mmol/L)	1.33	(0.93–1.97)	1.56	(1.15–1.98)	0.085#
TC (mmol/L)	5.11±1.00		5.14±1.12		0.842
LDL-C (mmol/L)	3.05	(2.45–3.79)	3.05	(2.47–3.71)	0.929
HDL-C (mmol/L)	1.37	(1.18–1.58)	1.40	(1.20–1.61)	0.493
UA (μmol/L)	341.30	(256.80–420.20)	299.10	(247.30–364.38)	0.027*
CCR (mL/min)	81.25±22.93		81.01±21.95		0.937
GLU (mmol/L)	5.39	(4.95–6.06)	5.43	(5.03–6.25)	0.486
Urine protein, n (%)	7	(9.72)	16	(7.27)	0.510
Occult blood, n (%)	1	(1.39)	2	(0.91)	>0.999
Concomitant medications					
Statins, n (%)	12	(16.67)	20	(9.09)	0.074#
ACEI, n (%)	4	(5.56)	16	(7.27)	0.617
ARB, n (%)	8	(11.11)	24	(10.91)	0.962
β-blockers, n (%)	7	(9.72)	5	(2.27)	0.015*

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Table 3 continued. Clinical features of different aspirin responsiveness groups.

	Aspirin hyporesponsive group (Ara-Q4, n=72)		Aspirin non-hyporesponsive group (Ara-Q1-3, n=220)		P-value
CCB, n (%)	26	(36.11)	68	(30.91)	0.412
Diuretics, n (%)	5	(6.94)	3	(1.36)	0.036*
Nitrates, n (%)	0	(0)	2	(0.91)	>0.999
Hypoglycemics, n (%)	7	(9.72)	31	(14.09)	0.339
PPI, n (%)	0	(0)	1	(0.45)	>0.999

Continuous variables are described as mean ±SD or median (interquartile range), whereas categorical variables are described as frequency (percent). # p<0.10, * p<0.05 BMI – body mass index; DM – diabetes mellitus; CHD – coronary heart diseases; PCI – percutaneous coronary intervention; Ara – arachidonic acid-induced platelet aggregation rate; WBC – white blood cell; RBC – red blood cell; Hb – hemoglobin; PLT – platelet; MPV – mean platelet volume; ALT – alanine aminotransferase; AST – aspartate transaminase; TG – triglyceride; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; UA – uric acid; CCR – creatinine clearance rate (according to Cockcroft formula); GLU – glucose; ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CCB – calcium channel blockers; PPI – proton pump inhibitors.

Table 4. The correlation between aspirin hyporesponsiveness and potential influencing factors.

			UA	β-blockers	Diuretics
Spearman's rho	Aspirin hyporesponsiveness	Correlation coefficient	0.132	0.162	0.147
		P-value	0.027*	0.006*	0.012*
		N	281	292	292

* p<0.05. UA – uric acid.

Table 5. The potential factors influencing aspirin hyporesponsiveness.

	B	SE	Wald	P-value	OR	95% lower	95% upper
Age	–0.050	0.026	3.568	0.059	0.951	0.904	1.002
Baseline Ara	0.029	0.013	5.311	0.021*	1.030	1.004	1.056
UA	0.003	0.002	4.319	0.038*	1.003	1.000	1.006
Statins	0.717	0.430	2.778	0.096	2.049	0.881	4.762
β-blockers	1.702	0.657	6.722	0.010*	5.487	1.515	19.870
Constant	–1.448	1.968	0.541	0.462	0.235		

* p<0.05. Ara – arachidonic acid-induced platelet aggregation rate; UA – uric acid; SE – standard error; OR – odds ratio

Table 6. The predictive value of potential influencing factors for aspirin hyporesponsiveness.

	AUC	SE	P-value	95% lower	95% upper
Baseline Ara	0.569	0.039	0.085	0.493	0.645
UA	0.588	0.041	0.027*	0.508	0.669
β-blockers	0.539	0.041	0.331	0.458	0.620

* p<0.05. Ara – arachidonic acid-induced platelet aggregation rate; UA – uric acid; AUC – area under the curve; SE – standard error.

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total of 292 elderly patients from 18 hospitals in China were included, which was somewhat representative of all elderly Chinese patients. There was an obvious decrease in Ara after taking aspirin. The extent of decrease in Ara after taking aspirin was positively correlated with age (r=0.145, p=0.013). However, the proportion of patients age ≥80 years in the aspirin hyporesponsive group (Ara-Q4) was not significantly different from that of the aspirin non-hyporesponsive group (Ara-Q1-3) (4/72, 5.56% *vs.* 9/220, 4.09%, p=0.846), probably because the number of patients age ≥80 years in each group was too small to show statistical power. Further large-scale clinical trials involving elderly patients are needed.

A recent study found that low-dose aspirin (75–100 mg) was effective in preventing cardiovascular events in participants weighting 50–69 kg, but was less effective in participants weighing 70 kg or more [20], suggesting that the administration of aspirin should be individualized depending on bodyweight. Golukhova et al. found BMI was an independent predictor of future aspirin hyporesponsiveness (OR: 1.003, 95% CI: 1.000–1.006, p=0.030) [21]. In this study, there were no significant differences in bodyweight ≥70 kg (32/72, 44.44% *vs.* 79/220, 35.91%, p=0.195) or BMI ≥28 kg/m^2 (11/72, 15.28% *vs.* 20/220, 9.09%, p=0.139) between the aspirin hyporesponsive group (Ara-Q4) and the aspirin non-hyporesponsive group (Ara-Q1-3), which might be due to race, age, and the small scale of the study.

Kapłon-Cieślicka et al. found smoking was an independent predictor of aspirin hyporesponsiveness (OR: 3.891, 95% CI: 1.052–14.391, p=0.042) [22]. In the present study, the proportions of smoking (13/72, 18.06% *vs.* 37/220, 16.82%, p=0.809) and smoking amount ≥20 pack-years (11/13, 84.62% *vs.* 23/37, 62.16%, p=0.251) in the aspirin hyporesponsive group (Ara-Q4) were not significantly different from the aspirin non-hyporesponsive group (Ara-Q1-3). A possible explanation is that the scale of the study was too small to show statistical power, and this topic warrants further investigation in large-scale studies.

In this study, the level of UA and the incidence of hyperuricemia were higher in the aspirin hyporesponsive group (Ara-Q4) than that in the aspirin non-hyporesponsive group (Ara-Q1-3). Spearman's correlation analysis showed that the level of UA was positively correlated with aspirin hyporesponsiveness (r=0.132, p=0.027). After multivariate adjustment, the results demonstrated the level of UA was independently and positively associated with aspirin hyporesponsiveness (OR: 1.003, 95% CI: 1.000–1.006, p=0.038), suggesting that increased UA level increases the risk of aspirin hyporesponsiveness. This is consistent with a previous study showing that the level of UA was an independent predictor of aspirin hyporesponsiveness (OR: 1.004, 95% CI: 1.000–1.007, p=0.048) [5]. A possible explanation is that the elevation of UA level promoted formation of a proinflammatory and prothrombotic state, with an increase in non-platelet-derived thromboxane A2 synthesis, leading to increased platelet aggregation and aspirin hyporesponsiveness [23]. ROC curve analysis demonstrated that UA level has limited predictive value for aspirin hyporesponsiveness (AUC: 0.588, 95% CI: 0.508–0.669, p=0.027), which might be related to the small scale of the study, and further validation in large-scale randomized controlled trials (RCT) is warranted.

Drug-drug interactions can affect the response to aspirin [24–26]. Bonten et al. found β-blockers significantly reduced platelet aggregation, which was synergistic with the response to aspirin [27], whereas Knight et al. found β-blockers enhanced platelet aggregation, which was antagonistic to the response to aspirin [28]. At present, there is still no consensus on the correlation between β-blockers and aspirin responsiveness. In this study, compared with the aspirin non-hyporesponsive group (Ara-Q1-3), the proportion of β-blockers use was significantly higher in the aspirin hyporesponsive group (Ara-Q4) (7/72, 9.72% *vs.* 5/220, 2.27%, p=0.015). Spearman's correlation analysis showed the use of β-blockers was positively correlated with aspirin hyporesponsiveness (r=0.162, p=0.006). Multivariate regression analysis demonstrated the use of β-blockers was independently and positively associated with aspirin hyporesponsiveness (OR: 5.487, 95% CI: 1.515–19.870, p=0.010). However, ROC curve analysis failed to show the value of β-blockers use for predicting aspirin hyporesponsiveness (AUC: 0.539, 95% CI: 0.458–0.620, p=0.331). It did not rule out the possibility that the scale of the study too small to achieve statistical significance, and this topic should be investigated further in large-scale clinical trials.

In this study, the ratio of diuretics use was higher in the aspirin hyporesponsive group (Ara-Q4) than in the aspirin non-hyporesponsive group (Ara-Q1-3) (5/72, 6.94% *vs.* 3/220, 1.36%, p=0.036), which is consistent with a previous study [5]. A possible mechanism is that diuretics use decreased the glomerular filtration rate [29], resulting in accumulation of harmful substances and increase of non-platelet-derived thromboxane A2 synthesis, which could lead to aspirin hyporesponsiveness. However, diuretics use was not entered into the regression equation after multivariate adjustment, perhaps because the number of patients using diuretics in this study was too small.

The strengths of this study are: (1) The studied elderly patients were included from nationwide hospitals, which is somewhat representative of all elderly Chinese patients; (2) Patients with aspirin monotherapy were included in this study, excluding the interference of other antithrombotic and antiplatelet medications on aspirin responsiveness; and (3) The main findings of this study were that baseline Ara, UA level, and β-blockers use were independently and positively associated with aspirin hyporesponsiveness. Large-scale RCTs are needed to further investigate this.

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The weaknesses of this study are: (1) The scale of this study was small, which might have affected the statistical power; (2) The number of patients age ≥80 years was small, which might have biased our results; and (3) The underlying mechanisms of potential factors influencing aspirin hyporesponsiveness were unclear and need to be investigated in large-scale RCTs.

Conclusions

This study found that: (1) the decreasing extent of Ara after taking aspirin was positively correlated with age; (2) baseline Ara, UA level, and β-blockers use were independently and positively associated with aspirin hyporesponsiveness in elderly Chinese patients. Our results need to be confirmed in large-scale clinical trials.

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Conflict of interest

None.

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