



Clinical characteristics, target organ damage and associate risk factors of resistant hypertension determined by ambulatory blood pressure monitoring in patients aged ≥ 80 years

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Abstract

Objectives To investigate clinical characteristics, target organ damage, and the associated risk factors of the patients aged ≥ 80 years with true resistant hypertension (RH). **Methods** Patients aged ≥ 80 years with hypertension ($n = 1163$) were included in this study. The included participants attended a structured clinical examination and an evaluation of RH was carried out. The prevalence, clinical characteristics and target organ damage of patients with RH were assessed. The associated clinical risk factors were analyzed by using logistic regression. **Results** The prevalence of RH diagnosis by 24-h ambulatory blood pressure monitoring assessment was 21.15%. End-diastolic left ventricular internal dimension, left ventricular mass index as well as prevalence of left ventricular hypertrophy were significantly greater in patients with RH than in control group. The common carotid artery intimal media thickness, carotid walls thickness, common carotid artery diameter and relative wall thickness were significant greater in RH group than in control. A relatively higher level of creatinine, estimated glomerular filtration rate, microalbuminuria and retinal changes was found in RH group than in control. A multivariate analysis showed that patients with a history of diabetes, higher body mass index (BMI) and lipid profiles were independent risk factors of RH. **Conclusions** The prevalence of RH in patients aged ≥ 80 years was within the range of reported rates of the general population. Subjects with RH diagnosis showed a higher occurrence of target organ damage than patients with well controlled blood pressure. Patients with diabetes, higher BMI and serum lipid profiles were independent risk factors for RH in patients aged ≥ 80 years.

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1 Introduction

Resistant hypertension (RH) is defined as inadequately controlled blood pressure (BP) despite a therapeutic plan that has included attention to lifestyle measures and prescription of ≥ 3 hypertension medications (ideally including a diuretic unless contraindicated), or controlled BP requires four or more antihypertensive drugs.^[1,2] Despite improvements in hypertension diagnosis and treatment, 30%–60% of hypertensive patients do not achieve BP targets and subsequently remain at risks for target organ damage.^[3] The

exact prevalence of RH is not easy to estimate as the difficulty and complexity in the diagnosis. The prevalence of RH in treated hypertensive population is widely variable with reported rates of 3% to 30%.^[4–6] Numerous factors such as obesity, obstructive sleep apnea, and primary aldosteronism, concurrent use of certain medications or substances and elevated activity of the sympathetic nervous system contribute to RH. Most of the clinical studies on RH excluded patients aged ≥ 80 years. The data on clinical characteristics, target organ damage, and the associated risk factors of the very old patients with RH are largely unknown. The present study aims to evaluate the prevalence of RH, target organ damage at different levels (heart, kidney and micro- and macro-circulation) and clinical risk factors of RH in the hospitalized patients aged ≥ 80 years.

2 Methods

2.1 Study population

Consecutive patients aged ≥ 80 years with hypertension

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admitted to our institution (Inpatient Department, Internal Geriatric Center of Chinese PLA General Hospital, Beijing, China) in 2011 were prospectively studied. Exclusion criteria were cardiovascular diseases (heart failure, unstable angina pectoris, acute coronary syndrome, life-threatening arrhythmia, atrial fibrillation, kidney failure, and grade III–IV retinopathy), intolerance to 24-h ambulatory blood pressure monitoring (ABPM), inability to comply with all study requirements, patients with advanced disease (cancer or non-cancer) in whom the initial estimate of life expectancy was less than three months, patients in whom follow-up availability was shorter than three months, and patients who were refusing to participate in this study.

The included participants attended a structured clinical examination and an interview carried out by a geriatrician and trained nurses. Demographic characteristics including sex, age, race, weight, height, waist circumference, medical histories, current diagnoses and drug use were collected. Cardiovascular risk factors [smoking, dyslipidemia, body mass index (BMI), diabetes, and physical inactivity] were recorded. All the participants attended a structured laboratory evaluation (glucose, cholesterol levels, renal function, serum K^+ , C-reactive protein and brain natriuretic peptide, and a sterile 24-h urine collection for micro-albuminuria, proteinuria and creatinine), 12-lead ECG, 2D-echocardiography, and carotid ultrasound. Written informed consent was obtained from the patients or the patients' close relatives. The study was approved by the Ethics Committee of Chinese PLA General Hospital (Beijing, China).

2.2 RH evaluation

The first step of evaluation of a patient with RH is exclusion of pseudoresistance. White-coat effect, inaccurate measurement techniques, non-adherence to pharmacologic treatments and a suboptimal medication regimen are common contributors of pseudoresistance.^[1] Firstly, we used 24-h ABPM to rule out white-coat effect. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate of patients were automatically assessed every 30 min for 48 consecutive hours with a properly calibrated Mobil O Graph (version 12) equipment. Non-adherence to pharmacologic treatments or non-pharmacologic therapy was evaluated through patient interview. The second step was to perform the assessment for secondary hypertension. Obstructive sleep apnea, medications, renal parenchymal disease was assessed in all patients. Definition of obstructive sleep apnea (apnea/hypopnea index ≥ 10) was corroborated by overnight polysomnography when the patient reported daytime sleepiness plus choking, loud snoring, interrupted breathing events, and/or awakenings during nighttime sleep. Medications and

substances that can increase BP mainly include nonsteroidal anti-inflammatory drugs, oral contraceptives, corticosteroids, anabolic steroids, erythropoietin and chemotherapeutic agents.^[7] Hypertension is common in chronic kidney disease (CKD). CKD is frequently observed in patients with hypertension. The presence of CKD was usually considered as a form of target organ damage. Patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min per 1.73 m² or with albuminuria ≥ 300 mg/24 h should be excluded because of renal parenchymal disease as secondary hypertension. eGFR was estimated by the chronic kidney disease epidemiology collaboration equation.^[8] Proteinuria was defined as either albumin/creatinine ratio ≥ 300 mg/g, or urinary albumin excretion ≥ 300 mg/24 h urine. Thyroid disease, hypercalcemia was evaluated depending on clinical presentation. After presence of pseudoresistance or secondary hypertension, the patient was ruled out.

2.3 Evaluation of target organ damage

Target-organ damage (left ventricular hypertrophy, left ventricular dysfunction, peripheral arterial disease, microvascular disease and renal dysfunction) were evaluated.

2.3.1 Echocardiography

M-mode, 2D and Doppler echocardiographic examinations were performed within the subjects. End-systolic and end-diastolic left ventricular internal diameter (LVIDd, LVIDs), interventricular septum thickness (IVST) and posterior wall thickness (PWT) were calculated from 2D guided M-mode tracing and measured during five consecutive cycles. Left ventricular mass (LVM) = $(0.8 \times [1.04 \times (LVID + IVST + PWT)^3 - (LVID)^3] + 0.6)$. Left ventricular hypertrophy (LVH) was defined as increased LVMI (≥ 96 g/m² in females and ≥ 116 g/m² in males). Left ventricular mass was estimated by Devereux's formula and normalized by body surface area. Relative wall thickness was calculated as $2 \times PWT/LVIDd$.

2.3.2 Carotid ultrasonography

Imaging of the bilateral extracranial carotid artery was obtained by a high-resolution linear array 10 MHz probe. The end-diastolic intima-media thickness of the posterior (far) wall of both common carotid arteries and the common carotid artery diameter were measured 5 mm, 10 mm, 15 mm, 20 mm, and 25 mm caudally to the bulb, then the measurements averaged. A plaque was defined as the presence of a focal thickening greater than 1.3 mm in any segment of extracranial carotid arteries. Intima-media thickening of common carotid artery was diagnosed using three different cut-offs: > 0.8 mm, > 0.9 mm, and > 1.0 mm.

2.3.3 Microalbuminuria

Urinary albumin concentration was measured by a radioimmunoassay kit (Scavo SPA, Cinisello Balsamo, Italy). The detection limit of the method was 0.5 mg/L. Microalbuminuria was defined as a urinary albumin excretion > 30 mg/24 h and 300 mg/24 h.

2.4 Retinography

All patients underwent a bilateral non-mydratric retinography. The printed images were evaluated by two physicians who did not know about the patients' clinical characteristics using the simplified Keith-Wagener-Barker (KWB) classification (classification I: diffuse arteriolar narrowing an arteriovenous ratio of at least 1: 2; classification II: abnormal arteriovenous crossing, any degree of depression of the vein in a crossing situated at more than one papillar diameter from the papilla; classification III: retinal haemorrhages or exudates).

2.5 Statistical analysis

Values were expressed as means \pm SD or percent. Statistical analysis was performed using SPSS software, version 20.0 for Windows (SPSS, Inc., Chicago, IL, USA). Mean values for patients with and without RH were compared using Student's *t*-test for independent samples. Chi-square statistics were used to compare categorical variables between groups. A multivariate logistic regression with RH as the dependent variable was performed to assess the independent associations of clinical parameters, after adjustment for other potentially important variables that could influence the prevalence of RH (age, BMI, medical history, duration of hypertension, glucose, lipid profile, and antihypertensive medication). The statistical significance was set at $P < 0.05$.

3 Results

In the present study, 1163 patients aged ≥ 80 years with hypertension were evaluated. Three hundred and nineteen patients with RH were identified according to the currently accepted definition, 844 patients whose BP were well controlled with ≤ 3 hypertension medications were included as the control group. Thirty nine patients with non-adherent to pharmacologic treatments and 38 patients having white-coat resistance were ruled out by clinical evaluation and 24-h ABPM. Two hundred and forty two patients were diagnosed with RH. One hundred and four patients with RH were diagnosed with secondary hypertension. At last, the remaining 138 patients (mean age: 88.3 ± 8.9 years) were true RH (flow chat of evaluation of resistant hypertension was presented in Figure 1). The prevalence of true RH was 21.15%

(242/1163) in patients aged ≥ 80 years with hypertension. Baseline clinical and laboratory characteristics of the subjects were listed in Table 1. Patients with RH had a higher incidence of coronary heart disease, stroke, and a significant higher level of glucose and serum lipids. Calcium-channel blockers, α - and β -blocker were more commonly prescribed in RH group. Age, diabetes, atrial fibrillation, heart rate, chronic obstructive pulmonary disease/asthma, known duration of hypertension, uric acid, and serum lipids did not differ significantly between RH group and non-RH group.

Subjects with RH diagnosis by 24-h ABPM show a higher prevalence of target organ damage than patients in control group. LVIDd, LVMI as well as prevalence of LVH were significantly greater in patients with RH than that in control. The common carotid artery intimal media thickness, carotid walls thickness, common carotid artery diameter and relative wall thickness were significant greater in the RH group than in controls. The prevalence of carotid plaques was not significantly higher in patients with RH as compared to controls (93% vs. 89%, $P > 0.05$).

A relatively higher level of creatinine, eGFR and microalbuminuria was found in the RH group than that in control. Albumin/creatinine ratio was significantly lower in the RH group. A very high rate of retinal changes was found both in RH and control, but a more advanced microvascular involvement was observed in RH group compared with control (51.4% and 21.7% RH patients had grade II and III retinopathy, respectively vs. 23.2 and 9.6% of controls).

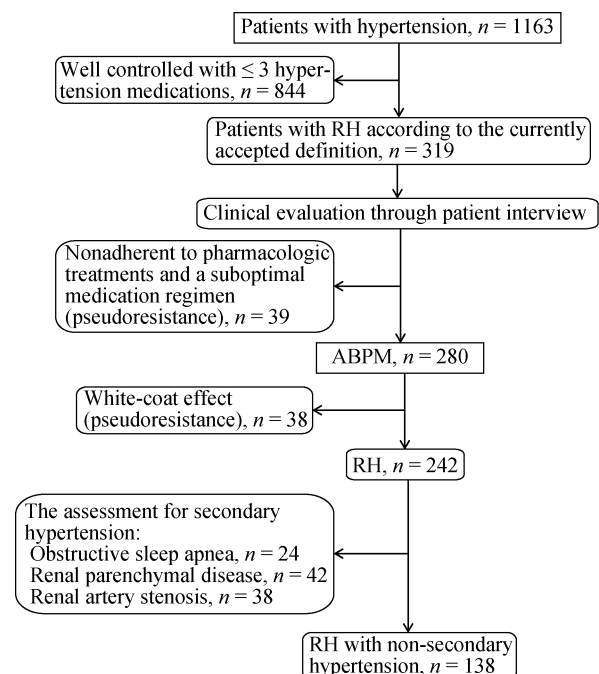


Figure 1. Flow chat of evaluation of RH. ABPM: ambulatory blood pressure monitoring; RH: resistant hypertension

Table 1. Baseline characteristics of the study population.

Characteristics	RH including secondary hypertension (242)	RH excluding secondary hypertension (n = 138)	Non-RH (n = 844)	P
Age, yrs	86.2 \pm 7.5	88.3 \pm 8.9	88.6 \pm 9.5	0.359
BMI, kg/m ²	27.92 \pm 2.73	27.31 \pm 3.60	25.21 \pm 3.37	< 0.001
Medical history				
Diabetes	101 (41.1%)	63 (45.7%)	329 (39.0%)	0.159
Coronary heart disease	71 (28.9%)	45 (32.6%)	197 (23.3%)	0.025
Atrial fibrillation	64 (26.01%)	41 (29.7%)	185 (21.9%)	0.050
Stroke/TIA	93 (37.8%)	49 (35.5%)	169 (20.0%)	< 0.001
COPD/Asthma	40 (16.3%)	20 (14.5%)	105 (12.4%)	0.492
Duration of HT, yrs	15 \pm 10.5	22.6 \pm 15.8	21.9 \pm 17.3	0.791
24-h SBP, mmHg	169.6 \pm 18.7	163.5 \pm 17.6	134.5 \pm 15.0	< 0.001
24-h SDP, mmHg	95.7 \pm 15.5	90.6 \pm 13.9	75.4 \pm 13.6	< 0.001
24-h HR, beats/min	85 \pm 14	83 \pm 15	80 \pm 17	0.853
24-h MAP, mmHg	109.8 \pm 13.8	114.9 \pm 15.1	95.1 \pm 10.6	< 0.001
Glucose, mg/dL	7.03 \pm 1.89	7.29 \pm 1.93	6.41 \pm 2.16	0.026
Total cholesterol, mmol/L	4.95 \pm 1.82	5.17 \pm 1.67	4.37 \pm 1.72	0.008
Triglycerides, mmol/L	2.85 \pm 1.60	2.95 \pm 1.58	2.07 \pm 1.62	0.013
HDL cholesterol, mg/dL	1.26 \pm 0.73	1.25 \pm 0.69	1.29 \pm 0.51	0.648
LDL cholesterol, mg/dL	2.55 \pm 0.71	2.68 \pm 0.75	2.24 \pm 0.82	0.007
Uric acid, mg/dL	336 \pm 67.53	347.18 \pm 120.78	345.72 \pm 86.43	0.658
Anti-hypertensive medication				
Calcium-channel blockers	71.5%	77.8%	69.5%	0.049
ACEI	20.5%	22.5%	19.8%	0.183
ARB	29.4%	25.8%	24.7%	0.546
α -blocker, %	29.3%	45.5%	20.4%	< 0.001
β -blocker, %	34.6%	39.7%	25.1%	< 0.001
Aldosterone antagonists	30.5%	38.9%	35.5%	0.376

Data are presented as means \pm SD or *n* (%) unless other indicated. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; HDL: high density lipoprotein; HT: hypertension; HR: heart rate; LDL: low density lipoprotein; MAP: mean arterial pressure; RH: resistant hypertension; SBP: systolic blood pressure; TIA: transient brain insufficiency.

Table 2. Target organ damage of RH determined by ambulatory blood pressure monitoring in patients aged ≥ 80 years.

	RH including-secondary hypertension (n = 242)	RH excluding-secondary hypertension (n = 138)	Non-RH (n = 844)	P
LVMI, g/m ²	137.6 \pm 25.6	133.9 \pm 25.6	101.2 \pm 11.5	< 0.001
LVH, %	75.2	71.5	30.6	< 0.001
CCA IMT, mm	1.1 \pm 0.4	1.0 \pm 0.3	0.8 \pm 0.3	0.042
CCA diameter, mm	6.5 \pm 0.5	6.3 \pm 0.7	5.7 \pm 0.6	< 0.001
RWT, mm	0.25 \pm 0.09	0.28 \pm 0.08	0.19 \pm 0.06	< 0.001
Prevalence of plaques, %	93	92	89	0.625
Creatinine, mg/dL	119.20 \pm 55.64	115.19 \pm 90.55	86.42 \pm 35.68	< 0.001
eGFR, mL/min per 1.73 m ²	65.27 \pm 32.16	71.16 \pm 30.15	92.64 \pm 26.39	< 0.001
Micro-albuminuria per 24 h, mg	20.68 \pm 30.56	25.81 \pm 34.92	11.75 \pm 13.43	< 0.001
Retinal changes				
KWB class I	59 (24.0%)	37 (26.8%)	567 (67.2%)	0.008
KWB class II	103 (41.9%)	71 (51.4%)	196 (23.2%)	0.004
KWB class III	84 (34.1%)	30 (21.7%)	81 (9.6%)	0.022

Data are presented as means \pm SD or *n* (%) unless other indicated. CCA: common carotid artery; eGFR: estimated glomerular filtration rate; IMT: intimal media thickness; KWB: Keith-Wagener-Barker; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index; RH: resistant hypertension; RWT: relative wall thickness.

After adjustment for age, BMI, medical history, duration of hypertension, SBP or DBP, glucose, blood lipids, uric acid, antihypertensive medication using a general linear model, a multivariate analysis showed that patients with a history of diabetes (OR = 2.35, 95%CI: 1.24–4.5; $P = 0.008$) and higher BMI (OR = 4.00, 95%CI: 1.50–10.61; $P = 0.005$), triglyceride (OR = 1.45, 95% CI: 1.10–1.99; $P = 0.016$), total cholesterol (OR = 1.80, 95%CI: 1.15–2.84; $P = 0.09$), and low density lipoprotein cholesterol (OR = 1.07, 95%CI: 1.013–1.136; $P = 0.015$) were independent risk factor for the occurrence of RH (Table 3).

4 Discussion

To our knowledge, the present study is the first to systematically investigate the prevalence, clinical characteristics and manifestations of target organ damage in a particularly selected group of patients aged ≥ 80 years with RH. Our results demonstrated that the prevalence of RH was 21.15% in patients aged ≥ 80 years with hypertension. Subjects with RH diagnosis by 24-h ABPM showed a higher occurrence of target organ damage than patients with well controlled BP. Patients with a history of diabetes, higher BMI and higher serum blood lipids were independent risk factors for RH in patients aged ≥ 80 years.

Population ageing is an increasing worldwide phenomenon due to a longer life expectancy. Among these elderly patients, the actual prevalence of RH is difficult to estimate. Patients included in the previous studies that estimated the prevalence of RH were almost no older than 80 years.^[4,6,9] Patients in this study had been provided with VIP health care services including individualized health exam and medical healthcare programs by high-quality specialists. The prevalence of RH in patients aged ≥ 80 years in the present study was consistent with that reported in the studies from various cohorts.^[9–12]

White-coat effect and medication nonadherence may be the common causes of pseudo-RH. In the present study,

13.57% (38/280) of the hypertensive patients were ruled out due to white-coat effect, 12.22% (39/319) of the included hypertensive patients were partially or completely non-adherent to pharmacologic treatments and a suboptimal medication regimen. The presence of white-coat resistant hypertension is common. ABPM was performed in-hospital, which could have contributed to the low proportion of white-coat RH. Several studies reported much higher prevalence of white coat resistant hypertension than our study. For example, Muxfeldt, *et al.*,^[13] estimated the prevalence of a significant white-coat effect was 37% of patients with RH. De la Sierra, *et al.*,^[9] reported that 37% of patients had white coat RH. Modolo, *et al.*,^[14] reported 49% of patients in their study with white coat RH. Strauch, *et al.*,^[15] reported that medication nonadherence among a cohort of patients with RH was 47%. Jung, *et al.*,^[16] found 53% of the patients were partially or completely non-adherent based on urinary assay for prescribed medications or their metabolites.

Our study demonstrated that patients with RH had higher prevalence of target organ damage at cardiac, carotid, retinal changes and micro-albuminuria than in control group. There are a plenty of studies reported higher prevalence of sub-clinical target organ damage in RH patients as compared with patients whose BP is under control.^[5,6,9,13,17]

The wall thickness normally increases in proportion to the increase in chamber radius. This type of hypertrophy is termed eccentric hypertrophy. In the case of chronic pressure overload, the chamber radius may not change; however, the wall thickness greatly increases as new sarcomeres are added in-parallel to existing sarcomeres. This is termed concentric hypertrophy. The most common type of LVH in RH group was concentric hypertrophy. On the contrary, eccentric hypertrophy appeared the most common pattern of LVH in the control group. The prevalence of LVH was much higher in RH group than in control group (71.5% vs. 30.6%). The prevalence of LVH was higher in our population of RH than that in the patients included in the LIFE study (71.5% vs. 42%).^[18]

Common carotid artery intimal media thickness, diameter and relative wall thickness in RH group were greater than that in control group. The European Lacidipine Study on Atherosclerosis study has shown that age, systolic and pulse pressures are the strongest determinants of carotid intimal media thickness.^[19] In our study, an extremely high prevalence of carotid plaques was found in both RH and control groups (92% and 89%, respectively).

Kidney damage represents a common event in the course of hypertension. The search for albuminuria and eGFR has become routine in the evaluation of subclinical renal damage. In our study, eGFR, micro-albuminuria per 24 h and

Table 3. Associate risk factors of RH determined by ambulatory blood pressure monitoring in patients aged ≥ 80 years.

Independent risk factor for resistant hypertension	OR (95% CI)	P
BMI	4.00 (1.50–10.61)	0.005
TG	1.45 (1.10–1.99)	0.016
TC	1.80 (1.15–2.84)	0.09
LDL-C	1.07 (1.013–1.136)	0.015
DM	2.35 (1.24–4.57)	0.008

BMI: body mass index; DM: diabetes mellitus; LDL-C: low density lipoprotein; RH: resistant hypertension; TC: total cholesterol; TG: triglyceride.

albumin/creatinine ratio were much higher in RH group than in control. The ability of eGFR, micro-albuminuria per 24 h and albumin/creatinine ratio for predicting increased cardiovascular and renal risk are well established on the basis of surveys in general population samples and in essential hypertensive patients.^[20,21]

In the present study, the prevalence of retinopathy was found much higher in RH group than in control group. It has been shown that there is a strong relation between retinal microvascular lesions and cardiac and macrovascular markers of target organ damage. The cause of RH is no doubt multifactorial. Excess fluid retention is thought to be the most common cause of RH. In our study, we found that a history of diabetes, higher BMI and lipid profile were independent risk factor for the occurrence of RH. It was reported that older age and higher BMI were associated with excess fluid retention.^[22]

Patients with RH have an overall higher mortality compared with nonresistant hypertension patients because subjects with RH have a worse cardiovascular and end-stage renal disease prognosis.^[11,23,24] Successfully lowering BP in RH may reduce hypertension-related cardiovascular events.^[25] Treatment of RH is largely predicated on intensification of diuretic therapy after failing to control BP. Several studies have reported the effectiveness of spironolactone as a fourth antihypertensive agent for treatment of RH.^[22,26,27] Patients with heart failure regularly taking spironolactone may contribute to the high proportion of patients using aldosterone antagonists in the present study. Several pharmacological regimens to treat such patients have inconsistent outcomes. It has been posited that the sympathetic nervous system and excess sodium intake are the principal drivers of RH.^[28] New treatment strategies including renal denervation, baroreceptor stimulation and new drugs are developing to improve BP control in RH.^[29]

There are some limitations of this study. Firstly, due to its cross-sectional nature, this study did not provide prognosis evidence of the very old patients with RH. However, our study is a large group of patients with 24-h ABPM data, which allowing identification of the clinical features that differentiate patients with true RH from control and from those with white coat RH. Secondly, the subjects were from a single health center and all of them were male. Thirdly, data of clinical trials based on ABPM-guided treatment are lacking. Intervention studies should be conduct to obtain adequate BP control to achieve the clinical prognosis in the future.

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