VHR-ASCVD in Chinese patients

Improvement of evaluation in Chinese patients with atherosclerotic cardiovascular disease using the very-high-risk refinement: a population-based study

Sha Li[1], Hui-Hui Liu[1], Yuan-Lin Guo[1], Cheng-Gang Zhu[1], Na-Qiong Wu[1], Rui-Xia Xu[1], Qian Dong[1], Jian-Jun Li[1,*]

[1] State Key Laboratory of Cardiovascular Disease, FuWai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Peking Union Medical College, BeiLiShi Road 167, Beijing 100037, China

ABSTRACT

Background: Continuous refinement of atherosclerotic cardiovascular disease (ASCVD) stratification has raised the definition of very-high-risk (VHR) recently, which has been underutilized in China. We aimed to identify patients at VHR and evaluate their performances in a Chinese population.

Methods: A total of 9944 patients with ASCVD was continuously enrolled. Patients at VHR was identified according to 2018 AHA/ACC guideline. Median follow-up was 36.4 months. Clinical characteristics, low-density lipoprotein cholesterol (LDL-C) achievements, and the prognostic value of VHR mapping for cardiovascular events (CVEs) were evaluated.

Findings: Overall, 26% (2542/9944) of patients were deemed as VHR, which were subsequently divided into two subgroups of VHR-1 [31% (779/2542)] and VHR-2 [69% (1763/2542)]. The rates of VHR were higher among patients of male (30%,2157/7268), young with age <45 years (46%,518/1130), and low-income regions (27%, 498/1838). Patients at VHR carried higher rates of risk factors than those at non-VHR (all p<0.001). However, only 3% (80/2542) of patients at VHR were prescribed with high-intensity of statins, and just 13% (321/2542) of them reached the LDL-C goal (<1.4mmol/L). Furthermore, of patients with coronary stenosis (n=9806), multiple-diseased vessels (47%, 1192/2523 *vs.* 36%,2587/7283) and occlusive lesions (36%, 902/2523 *vs.* 13%, 949/7283) were detected more commonly in those at VHR than non-VHR. The adjusted hazard ratios of VHR-1 and VHR-2 for primary CVEs were 2.58(1.61-4.14) and 2.23(1.55-3.20), respectively.

Interpretation: Our study firstly reported that patients at VHR carried more severe ASCVD burden, lower LDL-C achievement, and higher CVEs risk, suggesting that the refinement of ASCVD might be considered in China to further understand patients at VHR.

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1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is one of the leading causes of morbidity and mortality in China.[1] Current cholesterol guidelines have introduced and defined a subgroup of ASCVD at very-high-risk (VHR), which has approximately 3 times the risk of developing future ASCVD events than those at non-VHR.[2-4] Thus, timely and accurate refinement of ASCVD stratification is of vital importance for the treatment and prevention of cardiovascular consequences in clinical practice. Until now, the performance of patients with ASCVD meeting the definition of VHR among Chinese populations is unknown.

As far as we know, low-density lipoprotein (LDL) is causally related to ASCVD and that lowering LDL cholesterol (LDL-C) can significantly reduce the risk of ASCVD.[5] With the advancement of lipid-lowering drugs, the knowledge about LDL-C lowering has supported the concept that the lower the better, the earlier the better, and the longer the better.[6-7] Interestingly, a recent re-

* Correspondence to: Professor Jian-Jun Li, MD, PhD. State Key Laboratory of Cardiovascular Disease, FuWai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, China, Tel: 86+10+88396077; Fax: 86+10+88396584
E-mail address: lijianjun938@126.com (J.-J. Li).

port have suggested that the level of non-high-density lipoprotein cholesterol (non-HDL-C) is declining in many countries, but increasing conspicuously in China.[8] The latter presenting substantial rise in consumption of animal fats and continuous low prescription rates of statin should take the blame.[8] In fact, guidelines of China are relatively conservative and recommend the moderate-intensity statins as the dominant or initial treatment in clinical management.[9] The awareness, treatment, and achievement of LDL-C in Chinese population are largely insufficient.[10]

These situations highlight the huge gap between the less advanced epidemiological transition and the increasing and heavy disease burden in China. The recommended recognition of VHR from authoritative guidelines reinforces the need of further evaluation on Chinese patients with ASCVD. Hence, using a population-based data on patients with ASCVD, we sought to: 1) identify patients meeting the definition of VHR according to 2018 AHA/ACC guideline; 2) estimate the differences of risk factors pattern, treatment, LDL-C achievement, and coronary severity between patients at VHR and non-VHR; 3) assess the prognostic value of VHR mapping for adverse cardiovascular outcomes.

2. Methods

2.1. Study population

The present study complied with the Declaration of Helsinki and was approved by the hospital ethnic Committee (FuWai Hospital & National Center for Cardiovascular Diseases, Beijing, China).

From April 2011 through July 2018, we continuously enrolled a cohort of 9944 adults with established ASCVD in our division of FuWai hospital for the current analysis. Patients with ASCVD were those with chronic coronary artery disease (CAD), acute coronary syndrome (ACS), ischemic stroke, and/or peripheral arterial disease (PAD). Patients with severe levels of triglycerides (TG ≥5.6mmol/L), significant hematologic disorders, infectious or systematic inflammatory disease, thyroid dysfunction, severe liver/renal insufficiency and/or malignant disease were excluded from the study (supplemental Figure 1).

Demographic and clinical characteristics, data of laboratory assessment and routine coronary angiography (CAG) were collected from patients at baseline. We followed-up the cohort mapping for clinical outcomes until the study end date (February 26, 2019). The definition of ASCVD, co-morbidities, and endpoint events were consistent with the acknowledged standards and our previous studies.[11-12]

2.2. Socio-economic status, risk factors and CAD

Participants recruited in the present study were patients from all over the country, including high-income, middle-income, and low-income regions. The 3 socio-economic regions were defined by national criteria.[13] The details were as follows: patients with high income levels were from the Eastern region including 9 higher developed provinces named Beijing, Tianjin, Liaoning, Shandong, Jiangsu, Shanghai, Zhejiang, Fujian and Guangdong; with middle income levels were from the Central region including 10 provinces named Heilongjiang, Jilin, Hebei, Henan, Shanxi, Hubei, Hunan, Jiangxi, Anhui and Hainan; with low income levels were from the Western region including 12 lower developed provinces named Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia and Xinjiang.

Patients were classified into three groups (optimal, borderline, and elevated) according to 5 established and modifiable cardiovascular risk factors including hypertension, diabetes mellitus (DM), obesity, low high-density lipoprotein cholesterol (HDL-C),

and smoking respectively.[14-15] Blood pressure was considered optimal if systolic pressure was less than 120 mmHg and diastolic pressure was less than 80 mmHg, borderline if systolic pressure was 120 to 139 mmHg or diastolic pressure was 80 to 89 mmHg, and elevated if participant was with hypertension according to repeated blood pressure measurements ≥140/90 mmHg and/or taking anti-hypertensive drugs. Glucose tolerance was classified as normal, borderline if participant had impaired fasting glucose or impaired glucose tolerance, and elevated if participant was with diabetes as fasting serum glucose level of ≥6.99 mmol/L in multiple determinations and/or under active treatment with insulin or oral hypoglycemic agents. HDL-C was considered optimal if its level was more than 1.53 mmol/L, borderline was 1.04 to 1.53 mmol/L, and elevated was less than 1.04 mmol/L. Smoking status was categorized as optimal if participant was a nonsmoker, borderline was a former smoker, and elevated was a current smoker.

Obstructive CAD was defined as the detection of 50% to 99% diameter stenosis in any of the four major epicardial coronary arteries including left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA). Occlusive CAD was defined as 100% occlusion of the above vessels. Concentrations of plasma TG, total cholesterol (TC), HDL-C, LDL-C, apolipoprotein (apo) AI (apo AI), and apoB were measured using automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan). Of which, TG, TC, and HDL-C were measured by enzymatic assay while LDL-C was calculated by the Friedewald formula. Hemoglobin A1C (HbA1C) was measured using Tosoh Automated Glycohemoglobin Analyzer (HLC-723G8, Tokyo, Japan).

2.3. ASCVD risk classification

The classification of patients with ASCVD was evaluated according to 2018 AHA/ACC guideline.[4] Patients with VHR-ASCVD were identified if they met the definition of VHR: a history of ≥2 major ASCVD events (VHR-1) or 1 major event and ≥2 high-risk conditions (VHR-2). Patients without the above meetings were identified as those with non-VHR-ASCVD. Major ASCVD events included ACS within the past 12 months, history of myocardial infarction (MI) other than a recent ACS, history of ischemic stroke, and symptomatic PAD. High-risk conditions included age ≥65years, familial hypercholesterolemia or LDL-C ≥4.9mmol/L, prior coronary artery bypass grafting or percutaneous coronary intervention outside of the major ASCVD event(s), DM, hypertension, chronic kidney disease (eGFR 30–59 ml/min/1.73m^2), current smoking, persistently elevated LDL-C (≥2.6 mmol/L) despite maximally tolerated statin therapy, and history of congestive heart failure.

2.4. Statin therapy and LDL-C goal

The lipid-lowering therapy of patients was evaluated (supplemental Table 1). Since the pre-hospital use of ezetimibe was very low and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were unavailable on the market during our study period, we worked on statins as the lipid-lowering therapy. The intensity of statin therapy was divided into 3 categories:[4] high-intensity, moderate-intensity, and low-intensity. Target LDL-C of patients at VHR was defined less than 1.4 mmol/L and those at non-VHR was defined less than 1.8 mmol/L in the present study.

2.5. Follow-up and outcomes

After enrollment, all patients were actively followed-up with every 12-months interval through clinical visits and/or telephone contacts until February 2019 by well-trained nurses or cardiologists, who were blinded to the aim of this study. All available

Table 1
Baseline characteristics according to ASCVD stratification

N	VHR Total 2542	VHR-1 779	VHR-2 1763	Non-VHR 7402	P for trend
Male,%(n)	85% (2157)	87% (680)	84% (1477)	69% (5111)	<0.001
Hypertension,%(n)	71% (1799)	63% (494)	74% (1305)	63% (4630)	<0.001
Borderline blood pressure,%(n)	14% (355)	16% (128)	13% (227)	22% (1633)	<0.001
DM,%(n)	41% (1048)	37% (286)	43% (762)	30% (2254)	<0.001
Pre-DM,%(n)	41% (1047)	44% (340)	40% (707)	47% (3472)	<0.001
Obesity,%(n)	12% (300)	9% (73)	13% (227)	9% (688)	<0.001
Overweight,%(n)	51% (1299)	52% (405)	51% (894)	50% (3723)	<0.001
Low HDL-C,%(n)	55% (1388)	57% (446)	53% (942)	42% (3141)	<0.001
Borderline HDL-C,%(n)	39% (989)	36% (284)	40% (705)	47% (3478)	<0.001
Current smoking,%(n)	50% (1278)	46% (358)	52% (920)	33% (2452)	<0.001
Former smoker,%(n)	20% (520)	23% (178)	19% (342)	17% (1293)	<0.001
Family history of CAD,%(n)	31% (790)	31% (244)	31% (546)	32% (2380)	0.315
Length of hospitalization(days)	4(3-7)	5(3-7)	4(3-6)	4(3-5)	<0.001
Age(years)	58(48-65)	57(50-64)	58(47-66)	59(52-65)	<0.001
BMI(kg/m2)	26.0(24.2-28.1)	26.0(24.2-28.1)	26.0(24.2-28.3)	25.7(23.7-27.7)	<0.001
TG(mmol/L)	1.5(1.1-2.2)	1.5(1.1-2.1)	1.5(1.1-2.2)	1.5(1.1-2.1)	0.046
TC(mmol/L)	3.9(3.3-4.6)	3.9(3.2-4.6)	3.9(3.3-4.6)	4.0(3.3-4.7)	<0.001
LDL-C(mmol/L)	2.3(1.8-2.9)	2.3(1.8-2.9)	2.3(1.8-2.9)	2.4(1.8-3.0)	0.006
HDL-C(mmol/L)	1.0(0.8-1.2)	0.9(0.8-1.2)	1.0(0.8-1.2)	1.0(0.9-1.3)	<0.001
ApoAI (g/L)	1.3(1.1-1.4)	1.2(1.1-1.4)	1.3(1.1-1.5)	1.3(1.2-1.5)	<0.001
ApoB(g/L)	0.8(0.7-1.1)	0.8(0.7-1.1)	0.8(0.7-1.0)	0.8(0.7-1.0)	0.654

Data shown are %(n) or median (inter-quartile range). P values are shown for trend of "VHR-1 vs. VHR-2 vs. Non-VHR". AS-CVD, atherosclerotic cardiovascular disease; VHR, very-high-risk; VHR-1, subgroup of VHR with ≥2 major ASCVD events; VHR-2, subgroup of VHR with 1 major ASCVD events and ≥2 high-risk conditions; DM, diabetes; HDL-C, high-density lipoprotein cholesterol; CAD, coronary artery disease; BMI, body mass index; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo, apolipoprotein.

relevant data from any reported possible cardiovascular events (CVEs) were collected. Primary end points included cardiovascular death, nonfatal MI, and stroke. Secondary end points included unstable angina, unplanned revascularization or hospitalization in cardiology ward. After all, the data were obtained from 9783 patients and a total of 1651 recurrent events, including 1244 secondary events and 407 primary events were documented during a median of 36.4 months' follow-up.

2.6. Statistical analysis

Statistical analysis was performed with SPSS version 26.0 software (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant. Test of normality was performed by Kolmogorov-Smirnov test before comparison of continuous variable among groups. The variables including length of hospitalization, age, BMI, TG, TC, LDL-C, HDL-C, apoAI, and apoB among three ASCVD groups (VHR-1, VHR-2, non-VHR) did not subject to normal distribution (p<0.001). Therefore, median (inter-quartile range, IQR) was described and nonparametric trend-test among three AS-CVD groups was performed using Cruskal-Wallis test. Categorical variables were described as percentage (number) and differences were analyzed by chi-squared statistic test. To understand the prognostic value of VHR mapping for adverse cardiovascular outcomes, patients were followed-up and CVEs as described above were collected. Time-concomitant Cox regression model was used to test the hypothesis that the effect of covariates on survival rate did not change with time. The model was performed with the interactive item of time and the three ASCVD groups as time-varying covariate and ASCVD group, age, sex, income, hypertension, LDL-C, and DM as other covariates. The effect of the covariates on CVEs rate did meet the hypothesis (p>0.05). Based on the above prerequisite, event-free survival rate was estimated by Kaplan–Meier method and compared by log-rank test, and further Cox regression model was performed to calculate hazard ratio (HR) and 95% confidence interval (CI).

2.7. Role of the funding source

The funders had no role in data collection, analysis, or interpretation; study design; patient recruitment; decision to publish or preparation of the manuscript

3. Results

3.1. Proportions

As showed in Table 1, in patients with ASCVD, 26% (2542/9944) of them met the definition of VHR. The proportions of patients met VHR-1 or VHR-2 were 8% (779/9944), 18% (1763/9944) respectively. When grouped patients according to gender, age (supplemental Figure 2A), and socio-economic levels (supplemental Figure 2B), we found that the detection rates of VHR were higher in subgroups of men (30%, 2157/7268), young with age<45 years (46%, 518/1130), and low-income regions (27%, 498/1838).

3.2. Risk factors

As shown in Table 1, patients with VHR-ASCVD had the median age of 58 (IQR 48-65) years, and 85% (2157/2542) of them were men. Patients with non-VHR-ASCVD appeared older [59 (52-65) years, p <0.001] and the proportion rate of men was lower (69%, 5111/7402, p <0.001). The length of hospitalization decreased as the risk categorization of ASCVD decreased (p for trend <0.001).

Moreover, patients with VHR-ASCVD compared to those with non-VHR-ASCVD experienced higher rates of hypertension (71% vs. 63%), DM (41% vs. 30%), obesity (12% vs. 9%), hypo HDL-C (55% vs. 42%), and current smoking (50% vs. 33%). However, patients with VHR-ASCVD had lower rates of borderline risk factors including borderline high blood pressure (14% vs. 22%), pre-DM (41% vs. 47%), and borderline low HDL-C (39% vs. 47%) excepting for former smoking and overweight when compared to those with non-VHR-ASCVD.

Table 2
Proportions of patients stratified by coronary severity and ASCVD stratification

		VHR (N=2523)			Non-VHR (N=7283)		
		Total	Obstructive	Occlusive	Total	Obstructive	Occlusive
1-diseased vessel		*23%(581)*	*83% (485)*	*17% (96)*	*33% (2394)*	*96% (2291)*	*4% (103)*
	LM	0.7% (4)	75% (3)	25% (1)	0.8% (18)	94% (17)	6% (1)
	LAD	58% (339)	84% (285)	16% (54)	66% (1575)	97% (1525)	3% (50)
	LCX	16% (93)	89% (83)	11% (10)	16% (393)	96% (378)	4% (15)
	RCA	25% (145)	79% (114)	21% (31)	17% (408)	91% (371)	9% (37)
2-diseased vessels		*30% (750)*	*70% (523)*	*30% (227)*	*32% (2302)*	*90% (2073)*	*10% (229)*
	LM	2.8% (21)	76% (16)	24% (5)	3.1% (71)	100% (71)	0% (0)
	LAD	78% (585)	86% (505)	14% (80)	83% (1911)	96% (1831)	4% (80)
	LCX	57% (428)	82% (353)	18% (75)	56% (1296)	94% (1220)	6% (76)
	RCA	62% (466)	79% (370)	21% (96)	58% (1326)	93% (1230)	7% (96)
Multiple-diseased vessels		*47% (1192)*	*51% (613)*	*49% (579)*	*36% (2587)*	*76% (1970)*	*24% (617)*
LM		21% (248)	99.6% (247)	0.4% (1)	21% (535)	99.8% (534)	0.2% (1)
LAD		99.6% (1187)	81% (967)	19% (220)	99% (2563)	91% (2345)	9% (218)
LCX		98% (1169)	82% (953)	18% (216)	98% (2528)	90% (2282)	10% (246)
RCA		97% (1162)	71% (828)	29% (334)	97% (2501)	88% (2192)	12% (309)

Data shown are %(n). The respective first column data of VHR and non-VHR shown are proportions of patients with each number of diseased vessel (1-diseased vessel, 2- diseased vessels, multiple-diseased vessels) among total patients with CAD or each diseased coronary artery (LM, LAD, LCX, RCA) among patients with respective number of diseased vessel. The second and third column data of VHR and Non-VHR shown are proportions of patients with obstructive or occlusive lesion according to respective group of each line. ASCVD, atherosclerotic cardiovascular disease; VHR, very-high-risk; LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

3.3. Coronary stenosis

99% (2523/2542) of patients with VHR-ASCVD had CAD, and 98% (7283/7402) experienced CAD in patients with non-VHR-ASCVD. As shown in Table 2, of patients with CAD (n=9806), multiple-diseased vessels (47% *vs.* 36%) and occlusive lesions (36% *vs.* 13%) were detected more commonly in those at VHR than non-VHR (both p <0.001). The occlusive rate had an increase trend with number of the diseased vessels in both patients with VHR-ASCVD and non-VHR-ASCVD. Additionally, coronary stenosis in LAD was most often detected. The rates were lower in VHR-ASCVD than non-VHR-ASCVD among those with 1-diseased (58% *vs.* 66%) or 2-diseased (78% *vs.* 83%) vessels (both p<0.001). Almost all patients with multiple-diseased vessels could detect the LAD stenosis whether in VHR-ASCVD or non-VHR-ASCVD.

3.4. Treatment and goal achievement

Among patients with VHR-ASCVD, a pre-hospital statin was prescribed in 78% (1979/2542), the rate of moderate-intensity statin was 71% (1800/2542), and high-intensity statin was used by 3% (80/2542). While, a prior-statins was used in 70% (5199/7402) of patients with non-VHR-ASCVD. Only 2% (143/7402) of them was prescribed with high-dose of statins (Table 3).

Moreover, we concerned patients within subgroups divided according to sex, age, and socio-economic status (Table 3). In general, prior-statins were prescribed more common in patients of male, middle-age, and middle-income regions. The frequency of patients taking high-intensity statins ranged across these subgroups from 2% to 5% in those with VHR-ASCVD, and 1% to 2% in those with non-VHR-ASCVD.

As showed in Table 4, among patients at VHR, a target level of LDL-C<1.4mmol/L was reached by 13% (321/2542), while in patients at non-VHR, a target level of LDL-C<1.8 mmol/L was reached by 24% (1805/7402). Females had lower achievement rate of LDL-C than male patients (VHR 7% *vs.* 14%; non-VHR 19% *vs.* 27%; both p<0.001). The youngest-aged patients compared to the three old-aged groups had the highest rate of achievement at VHR (17% *vs.* 10% *vs.* 11% *vs.* 13%, p for trend =0.003) while the rates experienced no significant difference at non-VHR (21% *vs.* 25% *vs.* 24% *vs.* 25%, p for trend =0.345). There was no significant difference in achievement among subjects at VHR of different economic lev-

els, while the rates increased with the decreased economic levels in patients at non-VHR (22% *vs.* 25% *vs.* 27%, p for trend<0.001). Moreover, the attainment rate increased with the statin intensity (VHR 5% *vs.* 14% *vs.* 20%; non-VHR 13% *vs.* 31% *vs.* 53%; both p for trend<0.001). The rate of LDL-C achievement in those prescribed high-intensity statins was still low and the absolute number was small (20%, 16/80). Patients who prescribed moderate-intensity of statins, the dominant dose of statins in the present cohort, the target level was owed by only 14% (245/1800) of patients at VHR and 31% (1461/4708) of patients at non-VHR.

3.5. Outcomes

The rate of recurrent CVEs was highest in patients at VHR-1, followed by those at VHR-2 and non-VHR (primary events 8%,64/764 *vs.*6%,102/1737 *vs.* 3%,241/7282; secondary events 13%,99/764 *vs.* 14%,238/1737 *vs.* 12%,907/7282; Table 5). The cumulative incidence of primary CVEs was higher among patients who at VHR than among those at non-VHR (p<0.001, supplemental Figure 3A) while no significant difference in secondary CVEs (p=0.210, supplemental Figure 3B). The adjusted HRs with age, sex, income, hypertension, LDL-C, and DM for recurrent primary CVEs comparing patients at VHR-1, VHR-2 (*vs.* non-VHR) were 2.58 (1.61-4.14), 2.23 (1.55-3.20), respectively (both p<0.001, Table 5). The corresponding HRs across these groups for MI were 4.03 (1.67-9.73), 2.69 (1.26-5.74) respectively (both p<0.001); for stroke were 2.00 (1.00-4.28), 1.94 (1.13-3.34) respectively (p=0.04, 0.02 respectively); for mortality were 2.50(1.08-5.81), 2.38(1.25-4.51), respectively (both p<0.001, Table 5).

4. Discussion

To our knowledge, the current study firstly reported that proportion, risk factors pattern, and prognostic role of VHR in a Chinese population of ASCVD. The main findings were that patients at VHR carried more severe ASCVD burden, lower LDL-C achievement, and higher CVEs risk, suggesting that the refinement of AS-CVD might be considered in China to further understand patients at VHR.

The proportion of patients meeting the definition of VHR presented its own characteristics compared to the US population.[16-17] It reached a relatively low rate (26%), and was common in young

Table 3

Prior-statin according to age, sex, socio-economic status and ASCVD stratification

	Statin treatment		High intensity		Moderate intensity		Low intensity	
	VHR	Non-VHR	VHR	Non-VHR	VHR	Non-VHR	VHR	Non-VHR
Total	78% (1979)	70% (5199)	3% (80)	2% (143)	71% (1800)	64% (4708)	4% (99)	5% (348)
N	2542	7402						
Sex group								
Male	79% (1698)	72% (3666)	3% (64)	2% (103)	72% (1547)	65% (3336)	4% (87)	4% (227)
N	2157	5111						
Female	73% (281)	67% (1533)	4% (16)	2% (40)	66% (253)	60% (1372)	3% (12)	5% (121)
N	385	2291						
Age group								
<45 years	77% (399)	70% (428)	5% (28)	2% (12)	68% (352)	62% (381)	4% (19)	6% (35)
N	518	612						
45-54 years	82% (430)	71% (1356)	4% (19)	2% (46)	74% (389)	64% (1236)	4% (22)	4% (74)
N	525	1917						
55-64 years	79% (633)	71% (2105)	2% (20)	2% (57)	73% (584)	64% (1894)	4% (29)	5% (154)
N	802	2976						
≥65 years	74% (517)	69% (1310)	2% (13)	1% (28)	68% (475)	63% (1197)	4% (29)	4% (85)
N	697	1897						
Socio-economic group								
High income	78% (641)	71% (1802)	4% (29)	2% (55)	70% (578)	64% (1635)	4% (34)	4% (112)
N	826	2554						
Middle income	79% (966)	71% (2485)	3% (35)	2% (70)	72% (881)	64% (2250)	4% (50)	5% (165)
N	1218	3508						
Low income	75% (372)	68% (912)	3% (16)	1% (18)	68% (341)	61% (823)	3% (15)	5% (71)
N	498	1340						

Data shown are %(n). Number of patients with VHR or non-VHR in respective group of each line shown are N. ASCVD, atherosclerotic cardiovascular disease; VHR, very-high-risk.

Table 4

LDL-C achievements according to age, sex, socio-economic status and ASCVD stratification

	Total		High intensity of statin		Moderate intensity of statin		Low intensity of statin	
	VHR	Non-VHR	VHR	Non-VHR	VHR	Non-VHR	VHR	Non-VHR
Overall	13% (321)	24% (1805)	20% (16)	53% (76)	14% (245)	31% (1461)	5% (5)	13% (45)
N	2542	7402	80	143	1800	4708	99	348
SEX group								
Male	14% (293)	27% (1375)	19% (12)	58% (60)	15% (228)	33% (1114)	5% (4)	13% (29)
N	2157	5111	64	103	1547	3336	87	227
Female	7% (28)	19% (430)	25% (4)	40% (16)	7% (17)	25% (347)	8% (1)	13% (16)
N	385	2291	16	40	253	1372	12	121
Age group								
<45 years	17% (87)	21% (131)	14% (4)	50% (6)	20% (71)	29% (109)	0% (0)	9% (3)
N	518	612	28	12	352	381	19	35
45-54 years	10% (54)	25% (476)	16% (3)	52% (24)	11% (42)	31% (377)	5% (1)	16% (12)
N	525	1917	19	46	389	1236	22	74
55-64 years	11% (86)	24% (728)	25% (5)	51% (29)	10% (59)	31% (591)	3% (1)	15% (23)
N	802	2976	20	57	584	1894	29	154
≥65 years	13% (94)	25% (470)	31% (4)	61% (17)	15% (73)	32% (384)	10% (3)	8% (7)
N	697	1897	13	28	475	1197	29	85
Socioeconomic group								
High income	12% (96)	22% (570)	17% (5)	42% (23)	13% (75)	28% (463)	3% (1)	10% (11)
N	826	2554	29	55	578	1635	34	112
Middle income	13% (162)	25% (874)	23% (8)	61% (43)	14% (121)	31% (698)	4% (2)	13% (22)
N	1218	3508	35	70	881	2250	50	165
Low income	13% (63)	27% (361))	19% (3)	56% (10)	14% (49)	36% (300)	13% (2)	17% (12)
N	498	1340	16	18	341	823	15	71

Data shown are %(n). Number of patients with VHR or non-VHR in respective group of each line and column shown are N. LDL-C, low density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; VHR, very-high-risk.

patients (46%) rather than the elderly (27%). Sex difference displayed with male patients more likely to meet the definition than female ones (30% vs. 14%). While similar to the previous investigation,[16] those who lived in lower income regions were also found to have a relative higher rate of VHR-ASCVD. To further verify the proportion of VHR in Chinese population, more studies and large-sample data might be analyzed to formulate VHR in line with China's national conditions and population characteristics to acquire the specific guideline.

The burden of elevated ASCVD risk factors and coronary lesions was indeed higher or severe in patients with VHR-ASCVD.

However, both treatment and LDL-C achievement in this cohort were found to be surprisingly and worryingly low. Data on high-intensity statin therapy among Chinese patients with ASCVD was limited, only several small sample studies focused on patients with ACS supported the use of high-intensity statin therapy to improve the prognosis.[18-20] In contrast, our data suggested that the higher dose of statin was associated with the better achievement of LDL-C although the number of patients was small. Due to highly prevalent but poorly controlled situation in this populous country,[10] significant opportunity for improvement in cholesterol-lowering treatment and intensive studies focused on high-intensity

Table 5
Prognostic value of VHR in patients with ASCVD

		Events, %(n)	Adjusted HRs (95%CIs)	Events, %(n)	Adjusted HRs (95%CIs)	
Primary events	VHR-1	8.4% (64/764)	2.58(1.61-4.14)	13.0% (99/764)	1.05(0.77-1.43)	Secondary outcome
	VHR-2	5.9% (102/1737)	2.23(1.55-3.20)	13.7% (238/1737)	1.05(0.85-1.30)	
	Non-VHR	3.3% (241/7282)	1.00	12.5% (907/7282)	1.00	
MI	VHR-1	1.7% (13/764)	4.03(1.67-9.73)	3.7% (28/764)	1.09(0.66-1.85)	UA
	VHR-2	1.6% (28/1737)	2.69(1.26-5.74)	4.9% (85/1737)	1.17(0.82-1.68)	
	Non-VHR	1.0% (70/7282)	1.00	4.4% (318/7282)	1.00	
Stroke	VHR-1	3.0% (23/764)	2.00(1.00-4.28)	4.5% (34/764)	1.36(0.78-2.44)	Revascularization
	VHR-2	2.2% (39/1737)	1.94(1.13-3.34)	3.0% (52/1737)	1.05(0.66-1.65)	
	Non-VHR	1.7% (121/7282)	1.00	3.0% (222/7282)	1.00	
Mortality	VHR-1	3.7% (28/764)	2.50(1.08-5.81)	4.8% (37/764)	0.89(0.52-1.42)	Hospitalization
	VHR-2	2.0% (35/1737)	2.38(1.25-4.51)	5.8% (101/1737)	0.95(0.68-1.32)	
	Non-VHR	0.7% (50/7282)	1.00	5.0% (367/7282)	1.00	

Data shown are %(events/followed patients) and HRs(95%CIs) with adjustment for age, sex, income, hypertension, LDL-C, and DM performed by Cox regression analysis. The left corresponds to the primary events and the right corresponds to the secondary events. VHR, very-high-risk; ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; VHR-1, subgroup of VHR with ≥2 major ASCVD events; VHR-2, subgroup of VHR with 1 major ASCVD events and ≥2 high-risk conditions; LDL-C, low-density lipoprotein cholesterol; DM, diabetes.

of statins and/or combination with non-statin drugs such as eze-timibe and PCSK9 inhibitors seemed urgent among Chinese ASCVD adults, especially in those at VHR.[21-22]

Similar to the previous studies among US population,[16-17] patients with VHR-ASCVD had a rate of recurrent ASCVD events higher than their counterparts with non-VHR-ASCVD. Patients with VHR-1 or VHR-2 presented rates of nearly 3- or 2-times higher events than those with non-VHR-ASCVD. There was general consensus that the most of CVEs could be attributed to common and modifiable risk factors.[23] Our data indicated that the VHR, a more ominous ASCVD category, itself was an independent risk factor for predicting recurrent CVEs. Although one can argue about the definition applied to the current study mechanically, there was evidence that patients at VHR by the guideline really did carry a higher CVEs recurrence than those at non-VHR.

The current study had several potential limitations. First, the definition of VHR might be not completely accurate. For example, the condition of familial hypercholesterolemia was considered according to clinical diagnosis rather than genetic testing. Second, we defined the socio-economic status according to residents from high- (eastern), middle- (central), and low-income (western) regions rather than standardized protocols to approach households and individuals. Third, statin adherence and LDL-C levels following hospital discharge among this population were unavailable. Finally, the present study was a single-center nature with patients from nation-wide, but the sampling framework of this study might be not nationally representative.

In conclusion, the current study might replenish the knowledge of ASCVD refinement in China through the evaluation of VHR according to 2018AHA/ACC guideline. Patients at VHR should be identified in the initial screening of ASCVD for disease-definite diagnosis and clinical management, which appeared critical in Chinese population.

5. Contributors

LS, LHH, and LJJ conceived the study. LS and LJJ designed and programmed the study, and wrote the manuscript. GYL, ZCG, WNQ, XRX, and DQ collected the data and consulted on the analysis. All authors interpreted the results and approved the final version for submission.

Data sharing statement

LJJ have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Anyone who wishes to access the data of certain content to be determined can email to the corresponding author (LJJ: li-jianjun938@126.com)

Research in context

Evidence before this study

We searched PubMed for studies published before December, 2020, with the terms: ("extreme" OR "very high risk" OR "risk stratification" OR "risk model") AND ("atherosclerotic cardiovascular disease" OR" cardiovascular disease" or "coronary artery disease" or "coronary stenosis" OR "coronary atherosclerosis"). We restricted our search to studies published in English. Of 6426 articles retrieved, we identified no cohort studies investigating Chinese population with atherosclerotic cardiovascular disease (ASCVD) according to recent cholesterol guidelines. Since the creation of Framingham Heart Study in 1948, various risk prediction models have been continuously proposed and optimized, playing important roles in our understanding and prevention of CVD and its risk factors. In 2013, the concept of ASCVD was formally proposed and redefined by guideline, strengthening the overall disease risk management and clinical practice. Current guidelines even more directly define ASCVD at very-high-risk (VHR-ASCVD). During the past decades, rapidly economic development with unhealthy lifestyle and longer lifespan led to dramatic changes in the risk factors pattern and continuous upward trend of the incidence and mortality of ASCVD in China. However, there was a lack of data based on Chinese population for the VHR evaluation. Nevertheless, the real-world of VHR need to formulate the risk stratification in line with China's national conditions and population characteristics to guide the clinical practice.

Added value of this study

Our study is the first to show the proportion, risk factors pattern, and prognostic value of VHR in Chinese patients with ASCVD. The proportion of patients meeting the definition of VHR according to the 2018 AHA/ACC cholesterol treatment guideline was 26%. The burden of elevated CV risk factors and coronary lesions was indeed higher or severe in patients with VHR-ASCVD. While the statins use and low-density lipoprotein cholesterol (LDL-C) achievement in this cohort was found to be surprisingly and worryingly low. Our data supported the high-intensity of lipid-lowering treatment associated with better LDL-C achievement and lower ASCVD risk. Compared to those not at VHR, patients with VHR-ASCVD had a higher risk of recurrent ASCVD events.

Implications of all the available evidence

Our study validates the critical role of VHR in risk evaluation of ASCVD. The major and important implication of the available evidence is that patients at VHR carry more severe ASCVD burden and recurrent events risk. Those patients are who may need more attention to receive intensive lipid-lowering therapy and substantial ASCVD risk reduction, especially in Chinese population.

Declaration of Competing Interest

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2021.100286.

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