Supravalvular Aortic Stenosis and the Risk of Premature Death Among Patients With Homozygous Familial Hypercholesterolemia

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Patients with homozygous familial hypercholesterolemia (HoFH) have a high risk for premature death. Supravalvular aortic stenosis (SVAS) is a common and the feature lesion of the aortic root in HoFH. The relation between SVAS and the risk of premature death in patients with HoFH has not been fully investigated. The present study analysis included 97 HoFH patients with mean age of 14.7 (years) from the Genetic and Imaging of Familial Hypercholesterolemia in Han Nationality Study. During the median (±SD) follow-up 4.0 (±4.0) years, 40 (41.2%) participants had SVAS and 17 (17.5%) participants experienced death. The proportion of premature death in the non-SVAS and SVAS group was 7.0% and 32.5%, respectively. Compared with the non-SVAS group, SVAS group cumulative survival was lower in the HoFH (log-rank test, p <0.001). This result was further confirmed in the multivariable Cox regression models. After adjusting for age, sex, low density lipoprotein cholesterol (LDL_C)-year-score, lipid-lowering drugs, cardiovascular disease, and carotid artery plaque, SVAS was an independent risk factor of premature death in HoFH on the multivariate analysis (hazard ratio 4.45; 95% confidence interval, 1.10 to 18.12; p = 0.037). In conclusion, a significantly increased risk of premature death was observed in HoFH patients with SVAS. Our study emphasized the importance of careful and aggressive management in these patients when appropriate. **(Am J Cardiol 2021;145:58−63)**

HoFH is a rare autosomal co-dominant disease caused primarily by bi-allelic mutations of genes encoding low density lipoprotein receptor (LDLR; 95%), gene encoding apolipoprotein B (APOB; approximately 5%) and gene encoding proprotein convertase subtilisin/kexin 9(PCSK9; rarely).[1, 2] Recent study from the Netherlands estimated that the prevalence of HoFH was about 1:300,000 or higher in the western hemisphere.[3] Because of the reduced uptake and clearance of plasma low density lipoprotein cholesterol (LDL-C), patients with HoFH are characterized by hypercholesterolemia from birth and premature malignant atherogenesis before 20 years of age.[4] If left untreated, it is common that HoFH patients could generally not survive past 30 years old, due to atherosclerotic cardiovascular disease.[5] In HoFH, premature malignant atherogenesis induces endoluminal obstruction of the aortic root at the valvular and supravalvular level, which lead to supravalvular aortic stenosis (SVAS).[6] SVAS was a feature complication of HoFH. A large number of case reports and a limited number of cross-section studies have described the clinical characteristics of SVAS in HoFH.[7−10] However, few studies have explored the effect of SVAS on the long-term progression of HoFH patients, especially whether there is a direct relation between SVAS and premature death in patients with HoFH. As far as we know, just some case reports found that a few of HoFH patients with death had complications of SVAS. For example, Sprecher DL et al[11] reported that 2 HoFH with SVAS died before their third decades. It has not been fully investigated that whether HoFH patients with SVAS are at increased risk of premature death. Thus, the aim of the present study was to describe the clinical characteristics of the HoFH with SVAS and to evaluate the relation between SVAS and premature death in patients with HoFH.

Methods

The Genetic and Imaging of Familial Hypercholesterolemia (FH) in Han Nationality Study (trial registration #: ChiCTR1900022156) is an ongoing prospective cohort study designed to investigate the genes, imaging and other related risk factors and treatment of patients with FH in Han nationality. This cohort study was established by the "Zhenxin Team" affiliated to Beijing Anzhen Hospital in 2003. The recruited FH patients were diagnosed according to the Dutch Lipid Clinic Network (DLCN) Criteria[12] from multiple regions in China. Participants underwent

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standardized anthropometrics, interviewer-administered questionnaires, blood pressure, genetic testing, laboratory testing, including fasting lipid panel and blood glucose, and ultrasonic imaging examination, including echocardiography, carotid and achilles tendon ultrasonography upon enrollment. All of the participants were yearly followed with the same strategy to update the state of their health. Around 112 participants from above FH cohort (2003−2018) who met the HoFH diagnostic criteria were eligible for the present study. After excluding participants with missing follow-up information (n = 11), incomplete data of echocardiography (n = 2), liver transplantation surgery (n = 1), and aortic valve surgery (n = 1) the remaining 97 participants were included for the present study. The study protocol complied with the Declaration of Helsinki and was approved by Beijing Anzhen Hospital's institutional review board, and all participants provided written informed consent.

Two criteria were performed to the diagnosis of HoFH in the present study. The European Atherosclerosis Society criteria considers a diagnosis of possible HoFH as genetic confirmation of 2 mutant alleles at the LDLR, APOB, PCSK9, or LDLR Adaptor Protein1 gene locus or an untreated LDL-C >13 mmol/L (500 mg/dl) or treated LDL-C ≥8 mmol/L (300 mg/dl) together with either: cutaneous or tendon xanthoma before age 10 years or untreated elevated LDL-C levels consistent with heterozygous FH in both parents.[13] The Agenda for FH from the American Heart Association defines criteria for HoFH is that LDL-C ≥400 mg/dl (10 mmol/L) and 1 or both parents having clinically diagnosed FH, positive genetic testing for an LDL-C-raising (LDLR, APOB, or PCSK 9) gene defect, or autosomal-recessive FH, if LDL-C >560 mg/dl (14 mmol/L) or LDL-C >400 mg/dl (10 mmol/L) with aortic valve disease or xanthomata at <20 years of age or LDL-C >14 mmol/L without a family history of FH,or presence of 2 identical (true HoFH) or nonidentical (compound heterozygous FH) abnormal LDL-C-raising (LDLR, APOB or PCSK9) gene defects; includes the rare autosomal-recessive type.[14]

The diagnosis of SVAS is confirmed by transthoracic echocardiography. If the echocardiographic images of the participants meet the following 2 or more: the supravalvular aortic ring diameter < aortic valve annulus diameter or supravalvular aortic flow velocity >2.0 m/s or the presence of lump on the aortic root,[15−17] then the diagnosis of SVAS is established (Supplementary Figure 1).

The commercially available GE vivid7 system was used alternatively for 2-dimensional echocardiography and Continuous Wave Doppler (CW) imaging. The patients were examined in the left recumbent position. The parasternal long-axis view and an apical 5-chamber view were recorded for all patients with optimal gain and depth for imaging. The aortic valve annulus diameter and the supravalvular aortic ring diameter were measured in the parasternal long-axis view, which was recording at end-diastole by the upper parasternal approach. The supravalvular ring was defined as the narrowest site of the distal end of the sinus of valsalva. The presence of the lump on the aortic wall also was determined in the parasternal long-axis view. The supravalvular aortic flow velocity was evaluated by the maximal flow velocity just above the left ventricular outflow tract with the CW method in the apical 5-chamber view.

Ultrasonography was performed by Toshiba equipment (Applio500) with a 1 to 4 MHz transducer. The patient was examined in the supine position. Carotid intima media thickness was longitudinally measured 1 cm in front of the carotid bifurcation on the anterior and posterior wall of the right and left carotid artery . The intima media thickness of each stie was measured 3 times and the mean value was taken. Carotid plaques were defined as echogenic structures encroaching on the vessel lumen with a distinct area 50% greater than the intimal plus media thickness of adjacent sites.

Premature death was defined as all-cause death before the age of 70.[18]

Data on demographic variables such as age, sex, cutaneous or tendon xanthoma, arcus cornealis, cardiovascular disease (CVD) events (defined as history of unstable angina, myocardial infarction and/or coronary revascularization), lipid-lowering drugs taking, liver transplantation, and aortic valve surgery were collected using standardized questionnaire. Blood samples were collected from the antecubital vein after an overnight fast. Plasma total cholesterol, LDL-C, triglyceride and high-density lipoprotein cholesterol (HDL-C) were tested using routine commercial kits (Beckman Coulter, Brea, USA) and an automated biochemistry analyzer (Beckman AU 4500, Brea, USA) at the clinical laboratory of Beijing Anzhen Hospital. The LDL_C-year-score was calculated for each patient by multiplying the LDL-C (mmol/L) by the age at original diagnosis, to which was added the LDL-C value annually during follow-up.[19] Blood pressure was measured on the left arm using a mercury sphygmomanometer with a cuff of appropriate size following the standard recommended procedures. Two readings each of systolic blood pressure and diastolic blood pressure were taken at a 5-minute interval after participants had rested in a chair for at least 5 minutes. The average of the 2 readings was used for data analysis.

Continuous variables normally distributed were presented as mean ± standard deviation (SD). For those continuous variables lacking a normal distribution, median, and interquartile range was estimated. Mean values of continuous variables were compared with the student *t* test for independent data, whereas median values were compared with the nonparametric Mann-Whitney *U* test. Categorical variables were described as percentages and were compared using chi-square tests (χ^2 tests). Kaplan-Meier method was used to compare the cumulative survival in the Non-SVAS and SVAS groups. Multivariable Cox regression was performed to evaluate the relationship between the SVAS and premature death after adjusting for age, sex, LDL_C-year-score, lipid-lowering drugs, CVD, and carotid artery plaque. Statistical analysis was performed using SPSS, version 22.0 (IBM-SPSS, Chicago, Illinois). A 2-side p <0.05 was considered statistically significant.

Results

The baseline characteristics of the participants are shown in Table 1. During a median follow-up of 4.0 years, 41.2% participants had SVAS. The mean age of the participants was 14.7 years old. The proportion of arcus cornealis, CVD and carotid artery plaque were higher in group of HoFH patients with SVAS (p <0.05). In total, 96.9% (n = 94) of

Table 1
Baseline characteristics of the study participants

Variables	Non-SVAS (N = 57)	SVAS (N = 40)	p Value
Age (years)	12.1±11.4	18.5±10.5	<0.001
Men	42.1% (24)	60.0% (24)	0.083
SBP (mm Hg)	107.1±15.3	125.9±23.4	0.009
DBP (mm Hg)	65.6±9.1	73.1±17.1	0.055
TC (mmol/L)	17.1±4.7	16.6±3.3	0.571
TG (mmol/L)	1.2 (0.8-1.5)	1.3 (0.8-1.7)	0.315
LDL-C (mmol/L)	14.1±3.4	14.1±2.8	0.945
HDL-C (mmol/L)	1.1 (0.8-1.8)	1.3 (0.6-2.2)	0.857
LDL_C-year-score (mmol/L)	165.0±128.0	252.2±136.3	0.002
Cutaneous or tendon xanthoma	100% (57)	100% (40)	–
Arcus cornealis	28.1% (16)	67.5% (27)	<0.001
Lipid-lowering drugs	86.0% (49)	90.0% (36)	0.552
EF (%)	63.0 (60.0-68.0)	63.0 (58.0-68.0)	0.637
LA (mm)	26.0 (22.0-30.0)	32.0 (28.8-36.8)	<0.001
IVS (mm)	6.1 (5.0-8.0)	9.0 (6.7-10.0)	<0.001
LVPW (mm)	6.7 (5.0-8.0)	8.1 (7.0-10.0)	<0.001
CVD	15.8% (9)	55.0% (22)	<0.001
Carotid artery plaque	35.1% (20)	65.0% (26)	0.004
Aortic valve annulus diameter (mm)	13.9±3.8	15.3±3.1	0.152
supravalvular aortic ring diameter (mm)	18.3 (15.6-22.4)	17.7 (14.0-20.5)	0.348
Supravalvular aortic flow velocity (m/s)	1.3 (1.2-1.4)	2.6 (2.1-3.2)	<0.001
lump on the aortic wall	2.0% (1)	73.9% (17)	<0.001
Genetic mutations			0.187
LDLR alleles mutation	87.7% (50)	97.3% (36)	
LDLR+APOB mutation	10.5% (6)	2.7% (1)	
LDLR+PCSK9 mutation	1.8% (1)	0 (0.0)	
Follow-up(years)*	3.5±3.7	4.0±4.5	0.433

APOB = apolipoprotein B; DBP = diastolic blood pressure; EF = ejection fraction; IVS = interventricular septal thickness; HDL-C = high density lipoprotein cholesterol; LA = left atrial diameter; LDL-C = low density lipoprotein cholesterol; LVPW = left ventricular posterior wall thickness; CVD = cardiovascular disease; LDLR = low density lipoprotein receptor; PCSK9 = proprotein convertase subtilisin/kexin 9; SBP = systolic blood pressure; SVAS = supravalvular aortic stenosis; TC = total cholesterol; TG = triglyceride.

* Indicates median (±standard deviation).

the patients had a genetic test, only 3 patients did not have a genetic test but with a clinical diagnosis. The genetic causal mutations were found 88.7% (n = 86) in the LDLR alleles gene, 7.2%(n = 7) in the LDLR+APOB gene and 1.0% (n = 1) in the LDLR+PCSK9 gene.

There 17 cases of premature death in the participants, including 5 cases of sudden death and 12 cases of heart failure. The proportion of premature death was higher in the SVAS group (32.5%, p = 0.002; Figure 1).

Kaplan-Meier curves show the different trajectories of the proportion of cumulative survival across Non-SVAS and SVAS groups in HoFH along the entire follow-up (Figure 2). Cox proportional hazards models for SAVS and premature death are present in Table 2. In models that adjusted for cofounding factors, including age, sex, LDL_C-year-score, lipid-lowering drugs, CVD, and carotid artery plaque, SVAS was associated with increased risk for premature death with a hazard ratio of 4.45 (95% confidence interval, 1.10 to 18.12; p = 0.037).

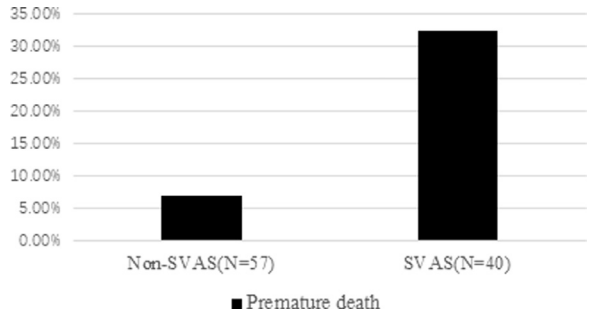

Figure 1. The proportion of premature death in Non-SVAS and SVAS groups. SVAS = supravalvular aortic stenosis.

Discussion

In present study, we evaluated the relationship between SVAS and premature death in patients with HoFH. Some clinical epidemiological features of SVAS in HoFH were found in the present study. Furthermore, a significantly increased risk of premature death was observed in HoFH patients with SVAS compared with patients without SVAS. Adjusting for confounders did not substantially attenuate this association.

SVAS was a characteristic cardiovascular manifestation of HoFH patients.[20–22] However, these studies were mostly clinical case reports. In these case reports, the age of HoFH patients with SVAS ranged from 2 to 61 years old.[7, 8] But no study results indicated the average age of HoFH patients with SVAS. The present study showed that the average age of SVAS in HoFH patients was 18.5 years old. This

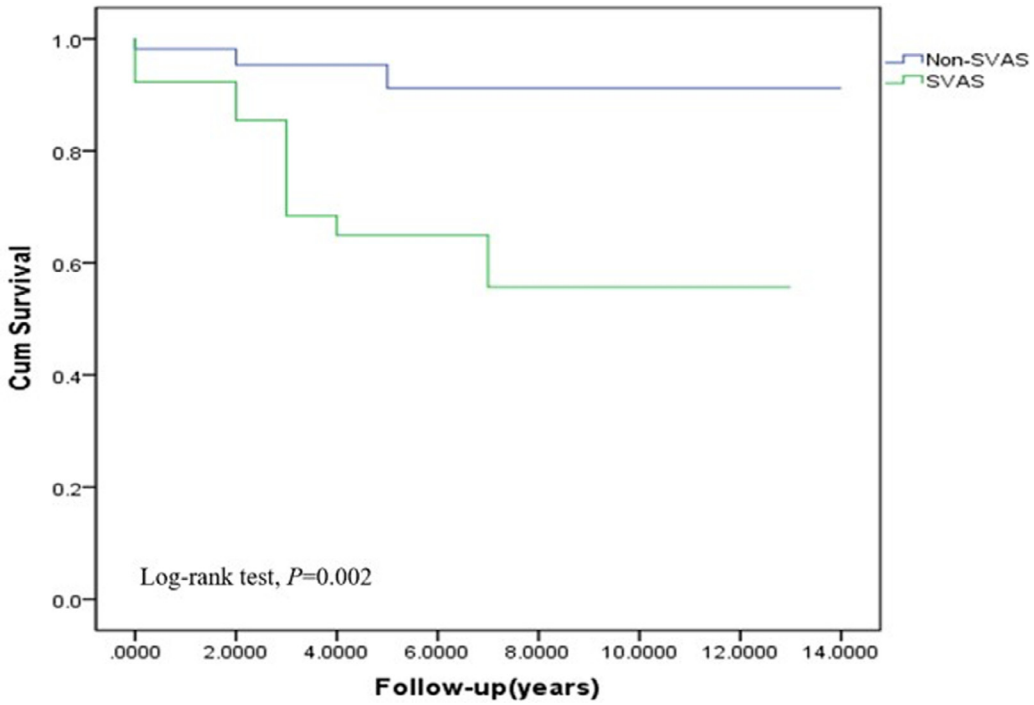

Figure 2. Kaplan−Meier estimates for the proportion of cumulative survival according to the SVAS groups in HoFH. SVAS = supravalvular aortic stenosis.

Table 2
Adjusted hazard ratios and 95% confidence intervals of premature death by SVAS groups

	Variables	B value	SE	Wald	HR (95%CI)	p Value
Model 1	SVAS	1.71	0.64	7.08	5.51(1.57-19.34)	0.008
Model 2	SVAS	1.68	0.66	6.44	5.36 (1.47-19.63)	0.011
Model 3	SVAS	1.49	0.72	4.35	4.45 (1.10-18.12)	0.037

CI = confidence interval; HR = hazard ratio; SE = standard error; SVAS = supravalvular aortic stenosis; Model 1: SVAS groups as the independent variables and premature death as the dependent variable. Model 2: Included variables in model 1 and adjusted for age (y) and sex. Model 3: Included variables in model 2 and further adjusted for LDL_C-year-score, lipid-lowering drugs, CVD and carotid artery plaque.

provided data basis for the clinical study of when HoFH patients may occur SVAS, which had a certain epidemiological significance. In addition, the current study demonstrated that HoFH patients with SVAS were more likely to develop arcus cornealis, CVD and carotid artery plaque. We believe that the mechanism of the arcus cornealis, CVD, and carotid artery plaque were the same as the SVAS owing to the arterial lipid deposition. Furthermore, our study results suggested that the incidence of SVAS in HoFH was 41.2%. Although, Brook et al[9] found that 3 of the 13 HoFH patients (23%) had SVAS by evaluating the aorta using 2-dimensional echocardiography. Beppu et al[10] also showed using echocardiography that all the 6 HoFH participants had severe SVAS. The main reason for the difference between our study results and the 2 studies may be the difference in sample size. The present study extended previous work and provide some clinical epidemiological data for the progression of SVAS in HoFH patients.

Premature coronary heart disease was the recognized leading cause of early death in HoFH.[23] Although, severe atheroma resulting in aortic root abnormalities was a also recognized typical complication of HoFH.[9] However, whether HoFH patients with SVAS are at increased risk of premature death has not been fully investigated. To our knowledge, several case reports have reported that sudden death of HoFH patients was related to SVAS. Sprecher DL et al[11] reported that 2 HoFH with SVAS died before their third decade. Mabuchi H et al[24] reported that 1 of 15 HoFH died of heart failure due to SVAS and ischemic cardiomyopathy. There were few cross-sectional or longitudinal studies of SVAS in HoFH patients. The present study provided a unique opportunity for a longitudinal evaluation of the risk of premature death in HoFH patients with SVAS. Our results suggested that HoFH patients with SVAS were more likely to have premature death than those without SVAS. Furthermore, we have demonstrated that after accounting for confounding factors, HoFH patients with SVAS had a 4.35 times higher risk of premature death compared with those without SVAS. These findings emphasized the importance of early detection and clinical treatment of SVAS to prevent the incidence of premature death in HoFH patients.

In HoFH, the atheromatous plaquing of the aortic root, occurs at an early age, results in SVAS. However, it is unclear that the cause of the SVAS in HoFH. Summers RM et al[25] believed that one possible explanation was that the atherosclerosis altered the growth of aortic vessel wall. On

the one hand, high LDL concentration might repress the expression of genes related to aortic growth. In contrast, the absence of normal LDL receptors arrested the growth of the ascending aorta. Because growing and proliferating cells express high levels of LDL receptors.[26–28] SVAS results in increased resistance to blood flow leading to elevated left heart pressure and cardiac hypertrophy, which might evolve to cardiac failure and death.[29]

Several limitations of our study should be noted. Although echocardiography has high value on diagnosing SVAS,[10] there are limitations to the measurement. We acknowledge that echocardiographic measurement data are somewhat subjective error. However, our research data were collected by system-trained sonographers and finally calibrated by the chief sonographer. What's more, as far as we know, there was lack of SVAS echocardiographic diagnostic criteria, which may bias the results of our study. But we defined SVAS based on the current relevant literatures on the different definitions of SVAS. Furthermore, the hazard ratio of the multivariate Cox regression model had wide confidence intervals, which due to our small sample size. However, HoFH of the type selected for this study is an exceptionally rare disorder, and as far as we know, the sample size of our present study was the largest compared to previous study on HoFH. Moreover, participants with sudden deaths were assumed to be most likely due to acute coronary syndrome, especially those without symptoms of typical angina. However, computed tomography coronary angiography and postmortem data were not available. In addition, the subjects were recruited from all over China, but due to the just for Han nationality, our results may not be generalizable to the entire Chinese population. Finally, the duration of the follow-up was relatively short, only 4 years. Strengths of our study include a longitudinal cohort study and a multicenter study.

Conclusion

Our study demonstrated that SVAS was a risk factor of premature death in patients with HoFH. Therefore, clinical strategies in these patients when appropriate are warranted.

Disclosures

The authors have no conflicts of interest to disclose..

Author Contributions

Ruiying Zhang: Investigation, data curation, conceptualization, methodology, writing original manuscript; Jinjie Xie: project administration; Jie Zhou, Liyuan Xu, Yufan Pan, Yichen Qu, Rongjuan Li, Mei Chong, Li Song, Wenhui Wen, Yue Wu and Jialu Li: Resources; Luya Wang: project administration, supervision and validation; Ya Yang: project administration, review and editing.

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Supplementary materials

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