Lipoprotein(a) is a risk factor for aortic and mitral valvular stenosis in peripheral arterial disease

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Aims	Lipoprotein(a) (Lp(a)) levels have been associated with aortic valvular calcification and stenosis. The prevalence and risk factors, including Lp(a) level, for valvular heart disease (VHD) were investigated in patients with peripheral arterial disease (PAD).
Methods and results	Echocardiography was performed in 861 patients with PAD to detect abnormal cardiac findings. Relationships between VHD and risk factors were analysed. The prevalence of VHD was 43.6%, and the prevalences of aortic valve regurgitation (AR), mitral valve regurgitation (MR), aortic valve stenosis (AS), mitral valve stenosis (MS), and tricuspid regurgitation (TR) were 26.8, 19.7, 5.9, 1.3, and 9.4%, respectively. In stepwise multiple regression analysis, severity of AR was related to age, albumin, and estimated glomerular filtration rate (eGFR); MR was related to eGFR and age; AS was related to eGFR, Lp(a), and age; MS was related to Lp(a) and female gender; and TR was related to age, body mass index, and total cholesterol (all $P < 0.05$). Lp(a) level was higher in patients with AS compared with those without AS [34.0 (16.7–50.0) vs. 20.0 (11.0–35.0) mg/dL, $P = 0.002$], in patients with MS compared with those without MS [37.0 (21.5–77.3) vs. 21.0 (11.0–35.0), $P = 0.037$], and in patients with AS and/or MS compared with those without AS and MS [34.0 (17.3–50.0) vs. 20.0 (11.0–35.0), $P = 0.001$]. Lp(a) levels were related to low-density lipoprotein cholesterol and high-sensitivity C-reactive protein levels ($P = 0.004$).
Conclusions	The high prevalence of VHD is found, especially in AR and MR, and the Lp(a) level is associated with increased risks of AS and MS in patients with PAD.
Keywords	peripheral arterial disease • valvular heart disease • lipoprotein(a) • aortic valve stenosis • mitral valve stenosis

Introduction

Cardiovascular diseases are major causes of death in patients with peripheral arterial disease (PAD).[1–3] Patients with PAD also complicate with diabetes mellitus, hyperlipidaemia, and hypertension, and may have severe systemic atherosclerosis that leads to mortality due to coronary artery disease (CAD).[1,3] PAD and a low ankle-brachial index (ABI) have also been associated with incident heart failure (HF).[4,5] This association suggests that many cases of HF are related to systemic atherosclerosis, including CAD, valvular heart disease (VHD), and hypertensive heart disease. However, the prevalence and risk factors for VHD in echocardiography are not fully understood in patients with PAD.

Lipoprotein(a) (Lp(a)) has a high degree of homology with plasminogen and is a risk factor for cardiovascular disease.[6] Lp(a) activates adhesion of monocytes and migration of macrophage foam cells into the arterial wall,[6,7] and Lp(a) levels are positively associated with coronary artery calcification and CAD events.[8–10] Several studies have recently shown that single-nucleotide polymorphisms (SNPs) in the Lp(a) locus are associated with aortic valvular calcification and stenosis.[11,12] However, the roles of serum Lp(a) as a potential risk factor for VHD are unclear in patients with PAD. Therefore, the purpose of this study was to investigate the prevalences of VHD and abnormal findings on echocardiography and to identify associated risk factors, including the Lp(a) level, in patients with PAD.

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Methods

Patients

The subjects were patients with PAD who were referred to the Cardio-vascular Hospital of Central Japan (Kitakanto Cardiovascular Hospital) between 1 January 2008 and 31 December 2014. Prior to the start of the study, the patients received a full explanation of the examination methods and gave written informed consent. The study protocol was approved by the Cardiovascular Hospital of Central Japan Medical Ethical Committee. The subjects were 861 consecutive patients with PAD and ABI < 0.90 at their first visit. The final diagnosis of PAD was based on clinical symptoms and iliac or femoropopliteal artery stenosis ≥70% on angiography or ultrasound. Clinical stages of PAD were classified using the criteria of the Inter-Society Consensus for the Management of Peripheral Arterial Disease.[1] ABI was determined in all subjects using ABI form (Colin, Tokyo, Japan), which simultaneously measures bilateral arm and ankle blood pressure by an oscillometric method.

Risk factors

Blood was collected during fasting in the morning to determine levels of Lp(a), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, albumin, glucose, glycated haemoglobin A1c (HbA1c), creatinine, remnant-like particle cholesterol, homocysteine, D-dimer, fibrinogen, thrombin−antithrombin complex (TAT), plasmin-α2 plasmin inhibitor complex (PIC), and high-sensitivity C-reactive protein (hs-CRP). The plasma levels of total cholesterol, triglyceride, HDL-cholesterol, creatinine, and glucose were measured using a standard autoanalyzer in the clinical laboratory at the Cardiovascular Hospital of Central Japan (Hitachi 7180 automatic analyzer; Hitachi High-Tech Fielding Co., Tokyo, Japan). The LDL-cholesterol level was calculated using the Friedewald formula. Serum Lp(a) was measured using a turbidimetric immunoassay. All other assays, including Lp(a) level, were performed at the Health Science Research Institute, Inc. (Saitama, Japan).

Diabetes mellitus, hypertension, stroke, and CAD were studied as risk factors for arteriosclerosis. Diabetes was defined as fasting plasma glucose >126 mg/dL for at least two measurements or a requirement for antidiabetes therapy. Hypertension was defined as blood pressure ≥140/90 mmHg recorded at least twice or intake of antihypertensive agents. The estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation for creatinine, as modified by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m²) = $194 \times (\text{Scr})^{-1.094} \times (\text{Age})^{-0287}$ (×0.739 if female).[13] Cerebral infarction was considered positive when the patient had a history of this condition or when lesions due to cerebral infarction were found in a brain CT scan. CAD was considered to be present when the patient had a history of this disease or showed a positive sign in stress/rest myocardial perfusion scintigraphy or coronary angiography.

Echocardiography

Echocardiography in all patients was performed in the ultrasound laboratory. Measurements were made after the subject had rested for at least 10 min in the supine position. Standard transthoracic echocardiography was performed with an Aplio SSA-770A and Artida SSH-880CV (Toshiba, Tokyo, Japan). Parasternal long-axis, apical four-chamber, two-chamber, and long-axis projections were obtained. Left atrial diameter and left ventricular end-diastolic and end-systolic diameters were measured. Haemodynamic parameters were obtained with pulsed-wave and continuous-wave Doppler ultrasound.

The severity of valve diseases was classified as mild, moderate, and severe, using the ACC/AHA Classification.[14] The classification for regurgitant and stenotic lesions was adapted from the recommendations of the American Society of Echocardiography.[15,16] Definitions of hypertensive heart disease and ischaemic heart disease were based on the recommendations for chamber quantification of the American Society of Echocardiography.[17]

Statistical analysis

Continuous variables are expressed as medians (interquartile range) and compared by the Wilcoxon test. Categorical variables are expressed as number (%) and compared by χ^2 test. The severities of VHD were categorized into four grades (nothing, mild, moderate, and severe). First, simple Pearson's correlations were calculated between the severities of VHD and all risk factors, including Lp(a). Next, factors with $P < 0.05$ in this analysis were evaluated using stepwise forward linear multiple regression analysis to examine relationships between the risk factors and severities of each VHD or Lp(a) levels. IBM SPSS Statistics ver. 22 (IBM Corp, Armonk, NY) was used for all calculations, with $P < 0.05$ considered to indicate a significant difference.

Results

Patient characteristics

The subjects were 861 patients with PAD. The median age was 73 (66–78) years. Clinical characteristics, including comorbidities and risk factors, are summarized in *Table 1*. The prevalences of VHD, ischaemic heart disease, and hypertensive heart disease were 43.6, 18.9, and 17.7%, respectively.

The prevalences of aortic valve regurgitation (AR), mitral valve regurgitation (MR), aortic valve stenosis (AS), mitral valve stenosis (MS), and tricuspid regurgitation (TR) were 26.8, 19.7, 5.9, 1.3, and 9.4%, respectively. The prevalences of each condition according to the severity of valve disease are shown in *Figure 1*. Congenital bicuspid aortic valve was found in two patients without AS or AR. Five patients had a history of artificial valvular replacement, including three with aortic valve replacement due to severe AR and two with mitral valve replacement due to severe MR. Three subjects had AS and MS, including one with severe AS and mild MS, one with moderate AS and mild MS, and one with mild AS and severe MS. No patients had a known history of rheumatic fever or carditis.

The clinical characteristics of patients with and without VHD are shown in *Table 1*. Patients with VHD included significantly more females and had significantly lower rates of smoking and alcohol intake; significantly higher age and homocysteine, D-dimer, TAT, and PIC levels; and significantly lower body mass index (BMI), eGFR, HbA1c, albumin, total cholesterol, triglyceride, and remnant-like particle cholesterol. Medical treatment did not differ significantly between the groups.

Risk factors for VHD

In Pearson's correlation analysis, AR had positive correlations with age, TAT, and PIC, and negative correlations with BMI, diabetes mellitus, eGFR, HbA1c, albumin, and triglyceride; MR had positive correlations with age, and negative correlations with eGFR, albumin, and triglyceride; AS had positive correlations with age, haemodialysis, and Lp(a), and negative correlations with eGFR; MS had positive correlations with age, female gender, and Lp(a), and a negative correlation with ABI; and TR had positive correlations with age,

Table 1 Baseline clinical characteristics and risk factors in patients with PAD with or without VHD

Risk factor	All patients, n = 861	VHD (+), n = 375 (43.6%)	VHD (−), n = 486 (56.4%)	P-value
Age (year)	73 (66−78)	76 (70−80)	71 (64−77)	<0.001
Gender (female)	180 (20.9%)	92 (24.5%)	88 (18.1%)	0.023
ABI	0.70 (0.51−0.80)	0.69 (0.51−0.80)	0.70 (0.52−0.80)	0.701
BMI (kg/m^2)	22.0 (19.7−24.3)	21.4 (19.1−24.0)	22.4 (20.3−24.5)	0.001
CLI	169 (19.6%)	81 (21.6%)	88 (18.1%)	0.226
Risk factors				
Hypertension	552 (64.1%)	238 (63.5%)	314 (64.6%)	0.774
Diabetes mellitus	295 (34.3%)	122 (32.5%)	173 (35.6%)	0.385
Coronary heart disease	324 (37.6%)	149 (39.7%)	175 (36.0%)	0.287
Cerebral infarction	163 (18.9%)	76 (20.3%)	87 (17.9%)	0.382
Smoking	619 (71.9%)	252 (67.2%)	367 (75.5%)	0.008
Alcohol intake	361 (41.9%)	136 (36.3%)	225 (46.3%)	0.003
Haemodialysis	75 (8.7%)	39 (10.4%)	36 (7.4%)	0.143
Laboratory data				
eGFR (mL/min/1.73 m^2)	54.3 (42.3−66.6)	50.2 (38.0−63.1)	57.4 (45.7−69.4)	<0.001
HbA1c (%)	5.7 (5.2−6.4)	5.6 (5.1−6.3)	5.7 (5.3−6.5)	0.014
Lp(a) (mg/dL)	21.0 (11.3−35.1)	21.0 (12.0−36.0)	20.4 (10.5−35.0)	0.300
Albumin (g/dL)	4.0 (3.8−4.2)	3.9 (3.6−4.1)	4.1 (3.8−4.2)	<0.001
Total-C (mg/dL)	183 (159−214)	181 (156−210)	185 (161−215)	0.039
LDL-C (mg/dL)	110 (88−136)	109 (89−135)	112 (88−137)	0.468
HDL-C (mg/dL)	47 (38−56)	47 (38−56)	46 (39−56)	0.923
Triglyceride (mg/dL)	119 (80−165)	108 (77−152)	128 (84−172)	<0.001
RLP-C (mg/dL)	5.7 (3.6−8.6)	5.4 (3.3−7.8)	5.9 (3.9−9.2)	0.001
Homocysteine (nmol/mL)	12.3 (9.5−16.1)	13.3 (10.1−17.0)	11.4 (9.1−15.6)	0.004
Fibrinogen (mg/dL)	307 (253−375)	311 (256−375)	305 (253−375)	0.723
D-dimer (μg/dL)	0.9 (0.5−1.9)	1.1 (0.6−2.3)	0.8 (0.5−1.6)	<0.001
TAT (ng/mL)	3.2 (2.0−6.0)	3.4 (2.2−6.5)	2.9 (2.0−5.8)	0.017
PIC (μg/mL)	1.0 (0.7−1.3)	1.1 (0.8−1.5)	0.9 (0.7−1.3)	<0.001
hs-CRP (mg/dL)	0.19 (0.08−0.51)	0.18 (0.09−0.55)	0.20 (0.08−0.50)	0.866
Drugs				
Statin	203 (23.6%)	79 (21.1%)	124 (25.5%)	0.145
Aspirin	437 (50.8%)	185 (49.3%)	252 (51.9%)	0.492
Thienopyridines	240 (27.9%)	97 (25.9%)	143 (29.4%)	0.248
Cilostazol	276 (32.1%)	125 (33.3%)	151 (31.1%)	0.508
Beraprost	326 (37.9%)	145 (38.7%)	181 (37.2%)	0.671
Sarpogrelate	65 (7.5%)	32 (8.5%)	33 (6.8%)	0.364
ACE	113 (13.1%)	44 (11.7%)	69 (14.2%)	0.310
ARB	206 (23.9%)	100 (26.7%)	106 (21.8%)	0.107
Ca antagonist	437 (50.8%)	188 (50.1%)	249 (51.2%)	0.783

ABI, ankle-brachial pressure index; BMI, body mass index; CLI, critical limb ischaemia; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin A1c; Total-C: total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; TAT, thrombin−antithrombin complex; PIC, plasmin-α2 plasmin inhibitor complex; hs-CRP, high-sensitivity C-reactive protein; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

fibrinogen, and PIC, and negative correlations with BMI, total cholesterol, LDL-cholesterol, and triglyceride (all $P < 0.05$).

In stepwise multiple regression analysis of disease severity, AR was related to age, lower albumin, and lower eGFR (A in Table 2); MR was related to lower eGFR and age (B in Table 2); AS was related to lower eGFR, Lp(a), and age (C in Table 2); MS was related to Lp(a) and female gender (D in Table 2); and TR was related to age, lower BMI, and lower total cholesterol (E in Table 2).

Lp(a) level in AS or MS and correlation with risk factors

The serum Lp(a) level was significantly higher in patients with AS compared with those without AS [34.0 (16.7−50.0) vs. 20.0 (11.0−35.0) mg/dL, $P = 0.002$, Figure 2], in patients with MS compared with those without MS [37.0 (21.5−77.3) vs. 21.0 (11.0−35.0) mg/dL, $P = 0.037$], and in patients with AS and/or MS compared with those without AS and MS [34.0 (17.3−50.0) vs.

20.0 (11.0−35.0) mg/dL, $P = 0.001$]. In Pearson's correlation analysis, the Lp(a) level had positive correlations with total cholesterol, LDL-cholesterol, and hs-CRP, and negative correlations with ABI and BMI. In stepwise multiple regression analysis, the Lp(a) level was positively associated with LDL-cholesterol and hs-CRP (*Table 3*).
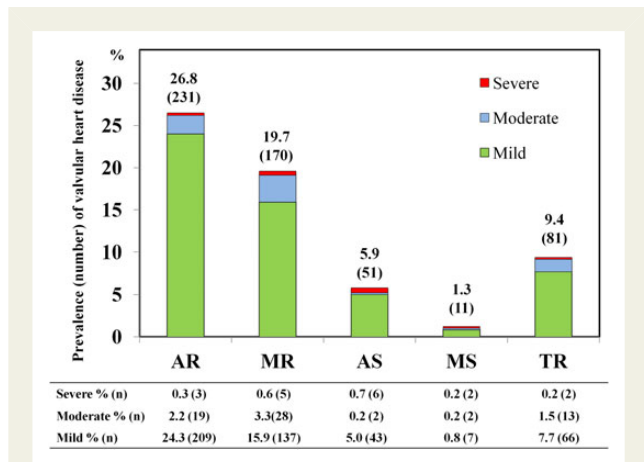

Figure I Prevalences (number) of each VHD classified as mild, moderate, and severe. AR, aortic valve regurgitation; MR, mitral valve regurgitation; AS, aortic valve stenosis; MS, mitral valve stenosis; TR, tricuspid regurgitation; n, number.

Discussion

This is the first report of the prevalence and risk factors, including Lp(a) level, for VHD and cardiac diseases analysed by echocardiography in patients with PAD. Older patients with valvular aortic stenosis have a higher prevalence of symptomatic PAD compared with those without aortic stenosis,[18] and patients with mitral annular calcification have a higher prevalence of low ABI compared with healthy controls.[19] However, to our knowledge, the prevalence of VHD has not been examined in patients with PAD. Our data suggest a high prevalence of VHD that was hidden in patients with PAD (median age 73 years). PAD has been associated with a two-fold increase in the prevalence of HF[20] and ABI ≤1.00 in a middle-age community cohort was found to have an increased risk for HF, independent of traditional HF risk factors, coronary heart disease, carotid atherosclerosis, and myocardial infarction.[4] Thus, asymptomatic VHD may be a precursor of symptomatic HF.

In this study, the prevalences of AR and MR were higher than those of other VHDs. Idiopathic dilatation of the aorta, congenital abnormalities of the aortic valve, and calcific degeneration are common causes of AR,[14] whereas those for MR include mitral valve prolapsed syndrome, rheumatic heart disease, CAD, and infective endocarditis.[14] In our study, severity of AR was related to age, lower albumin, and lower eGFR, and that of MR was related to lower eGFR and age. Age and chronic kidney disease are important risk factors for systemic atherosclerosis[21−23] and patients with diabetic renal disease have a higher prevalence and severity of vascular and

Table 2 Correlations between severity of VHDs and risk factors in multiple regression analysis

Risk factor	β	B	95% CI	P-value
A[a]				
Age	0.195	0.010	0.006−0.013	<0.001
Albumin	−0.124	−0.149	−0.244 to −0.053	0.002
eGFR	−0.089	−0.002	−0.003 to 0.000	0.024
B[b]				
eGFR	−0.116	−0.003	−0.004 to −0.001	<0.001
Age	0.119	−0.007	0.003−0.010	0.001
C[c]				
eGFR	−0.108	−0.002	−0.003 to −0.001	0.003
Lp(a)	0.101	0.001	0.000−0.003	0.006
Age	0.080	0.003	0.000−0.005	0.028
D[d]				
Lp(a)	0.138	0.001	0.001−0.002	<0.001
Female gender	0.087	0.045	0.008−0.0081	0.017
E[e]				
Age	0.150	0.006	0.003−0.009	<0.001
Body mass index	−0.142	−0.017	−0.023 to −0.007	<0.001
Total cholesterol	−0.114	−0.001	−0.002 to 0.000	0.004

A, aortic valve regurgitation; B, mitral valve regurgitation; C, aortic valve stenosis; D, mitral valve stenosis; E, tricuspid regurgitation; β, standardized partial regression coefficient; B, partial regression coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate.
[a]$R^2 = 0.301$, F for change in $R^2 = 5.096$, $P < 0.001$.
[b]$R^2 = 0.193$, F for change in $R^2 = 10.633$, $P = 0.001$.
[c]$R^2 = 0.132$, F for change in $R^2 = 4.868$, $P < 0.001$.
[d]$R^2 = 0.143$, F for change in $R^2 = 5.726$, $P = 0.017$.
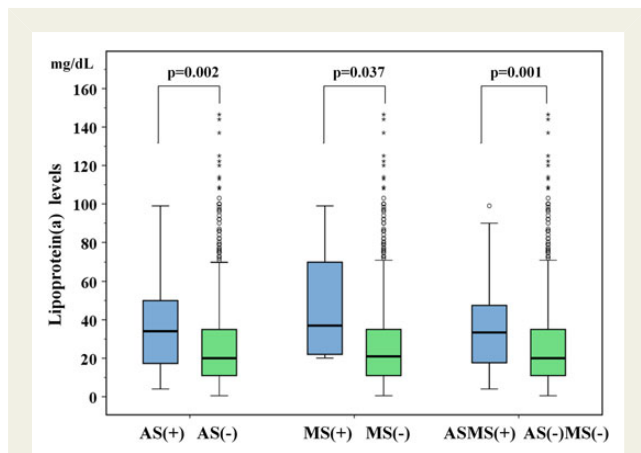[e]$R^2 = 0.154$, F for change in $R^2 = 8.568$, $P < 0.001$.

Figure 2 Non-parametrical comparison of Lp(a) levels in patients with or without AS (left), with or without MS (middle), and with AS and/or MS [ASMS(+)] and without AS and MS [AS(−)MS(−), right].

Table 3 Correlations between Lp(a) and risk factors in stepwise forward multiple regression analysis

Risk factor	β	B	95% CI	P-value
LDL-cholesterol	0.108	0.078	0.019 to 0.129	0.008
hs-CRP	0.083	1.213	0.032 to 2.303	0.044

$R^2 = 0.276$, F for change in $R^2 = 4.079$, $P = 0.004$.
β, standardized partial regression coefficient; B, partial regression coefficient; CI, confidence interval; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

valvular calcifications compared with non-diabetic controls.[24] Degenerative calcification of the aortic and mitral valves has also been reported to be more common in patients with end-stage renal failure.[25]

Albumin is an important and widely used nutritional marker and a negative acute-phase protein with a reduced level in inflammatory processes,[26–28] during which inflammatory cytokines, including interleukin-1 and interleukin-6, induce the acute-phase response.[29,30] Therefore, a low serum albumin level is associated with a higher risk of myocardial infarction, stroke, and all-cause mortality.[26–28] Furthermore, malnutrition and chronic inflammation are common in patients with chronic renal failure and are linked to poor cardiovascular outcomes.[31,32] Thus, chronic kidney disease, lower albumin level, and aging may be risk factors for aortic and mitral valvular regurgitation.

AS was related to lower eGFR, Lp(a) level, and age, and MS was related to the Lp(a) level and female gender. The most common cause of AS in adults is calcification of a normal trileaflet or congenital bicuspid valve, and this calcific AS is an active disease process characterized by lipid accumulation, inflammation, and calcification, with many similarities to atherosclerosis.[14] Lp(a) levels are associated with aortic valvular calcification and stenosis.[33,34] Lp(a) is a

cholesterol-rich particle consisting of a molecule of apolipoprotein B100 covalently linked with a molecule of apolipoprotein(a).[6] In this study, the Lp(a) level had a positive correlation with LDL-cholesterol and hs-CRP. Lp(a) activates adhesion of monocytes and uptake of macrophage foam cells into the arterial wall, and induces plaque inflammation.[6,7] Lp(a) levels are associated with coronary artery calcification and CAD events,[7–10] and several studies have recently shown that SNPs in the Lp(a) locus are associated with aortic valvular calcification and stenosis.[11,12] Elevated Lp(a) levels and the corresponding genotypes are associated with an increased risk of AS in the general population.[12] The results of our study also suggest that elevation of the Lp(a) level and inflammation are risk factors for AS in patients with PAD.

This is the first report of a correlation between serum Lp(a) level and MS. The main causes of MS are rheumatic carditis, chest radiotherapy, drug-induced mitral valve disease, anti-phospholipid syndrome, mucopolysaccharidosis, and severe annular calcification.[14] SNPs have been associated with mitral annular calcification evaluated on CT scans.[11] Thus, an elevated Lp(a) level may also be a risk factor for MS, similarly to AS, in patients with PAD. In the current study, female gender was a second independent risk factor for MS, and there was a higher proportion of females among patients with VHD compared with those without VHD. In patients with PAD, symptomatic conditions were more severe in females, including older age and more frequent diabetes mellitus and hyperlipidaemia.[35,36] These risks may be a cause of VHD, including MS, characterized by lipid accumulation and calcification, similarly to atherosclerosis.

TR had positive correlations with age and negative correlations with BMI and total cholesterol. The main causes of TR are rheumatic valvulitis, infective endocarditis, radiation therapy, tricuspid valve prolapse, tricuspid annular dilatation, or left-sided heart disease or pulmonary hypertension in the absence of organic lesions of the tricuspid valve.[14,37] In chronic HF, BMI in patients with severe or moderate TR is lower than that in those with mild TR or a normal tricuspid valve.[38] TR also had negative correlations with triglyceride and LDL-cholesterol levels. Thus, aging and malnutrition are risk factors for systemic atherosclerosis and may be risk factors for TR in patients with PAD.

Study limitations

The limitations of this study include the relatively small sample size and the performance of the study at a single facility. The design of this study was cross-sectional analysis. Also, we did not analyse SNPs, and we did not use population-based data. Therefore, further studies are needed to determine the exact prevalence and risk factors for VHD in patients with PAD.

Conclusion

The prevalence of VHD was markedly higher, especially in AR and MR, in patients with PAD. Elevated Lp(a) levels were associated with an increased risk of AS and MS in patients with PAD.

Conflict of interest: none declared.

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