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Long-Term Prognosis and Predictive Risk Factors for Polyvascular Disease in Patients with Peripheral Arterial Disease

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Abstract

Background: The aim of the current study was to assess fifteen-year life expectancy, cardiovascular events, fate of the limb, and risk factors with or without polyvascular disease in patients with Peripheral Arterial Disease (PAD). **Methods:** We conducted a prospective cohort study in 1019 PAD patients. The endpoints were Cardiovascular or Cerebrovascular Death (CCVD), All-Cause Death (ACD), Major Adverse Cardiovascular Events (MACE), and Cardiovascular and/or Limb Events (CVLE). **Results:** The patients who died were 539 (52.9%) during follow-up periods. The rate of CCVD was 50.5% (n = 272). In multiple regression analysis, the number of affected arteries had correlations with estimated Glomerular Filtration Rate (eGFR), HDL-cholesterol, Ankle Brachial Pressure Index (ABI), and diabetes ($p < 0.05$). In multiple logistic analysis, PAD with Cerebrovascular Disease (CVD) was correlated with older age, ABI, eGFR, and atrial fibrillation ($p < 0.05$); PAD with Coronary Heart Disease (CHD) was correlated with younger age, eGFR, HDL-cholesterol, LDL-cholesterol, and diabetes ($p < 0.05$); and triple vascular disease (PAD with CVD and CHD) was correlated with ABI, eGFR, HDL-cholesterol, and diabetes ($p < 0.05$). The number of affected arteries had significant correlations with CCVD, ACD, MACE, and CVLE ($p < 0.05$). In Cox multivariate analyses, age, Critical Limb Ischemia (CLI), eGFR, albumin, C-Reactive Protein (CRP), Body Mass Index (BMI), CVD, and CHD were related to CCVD ($p < 0.05$); age, albumin, eGFR, CRP, BMI, CLI, and CVD were associated with ACD ($p < 0.05$); age, albumin, eGFR, CRP, CLI, CHD, and diabetes were associated with MACE ($p < 0.05$); age, ABI, albumin, eGFR, CRP, CLI, CHD, and diabetes were related

to CVLE (p < 0.05). Statins improved all outcomes (p < 0.05). **Conclusions:** Polyvascular disease was independently associated with fifteen-year mortality, cardiovascular events, and the fate of the limb with diverse risk factors in PAD patients.

Keywords

Polyvascular Disease, Cerebral Infarction, Coronary Heart Disease, Fate of Leg, Peripheral Arterial Disease

1. Introduction

Polyvascular disease is defined as a coexistent arterial disease in two or three territories (cerebral, coronary, and/or peripheral) within each patient [1]. Patients with Peripheral Arterial Disease (PAD) complicate with severe systemic atherosclerosis that causes mortality due to Cerebrovascular Disease (CVD) and Coronary Heart Disease (CHD) [2] [3] [4] [5]. Since atherosclerosis is a systemic disease process, recent attention has focused on the coincidence of PAD with atherosclerosis in other arterial beds, most commonly CHD and CVD. In the Reduction of Atherothrombosis for Continued Health (REACH) Registry [6], the prevalence complicated with other arterial diseases was 22.4% in CHD (PAD and/or CVD) and 23.0% in CVD (PAD and/or CHD), whereas that was 43.8% in PAD (CVD and/or CHD) [7]. Moreover, several studies have reported that half of the patients with PAD have concomitant CHD [2] [8] [9]. We have found the prevalence of asymptomatic CVD is extremely high and CVD is an independent risk factor for long-term survival and aggravation of limb stages in PAD patients [10] [11]. Thus, patients with PAD have the most severe systemic atherosclerosis that causes higher morbidity and mortality among these three vascular diseases [12] [13]. In addition to the high mortality risk due to CHD and CVD, there is a higher probability of acute limb ischemia, revascularization, and amputation in patients with atherosclerosis of lower limb vessels among PAD patients with polyvascular disease [14].

Several studies have reported risk factors for concomitant vascular diseases in PAD patients including PAD alone (PADa), double vascular diseases (DoVD: PAD with CVD or CHD), and triple vascular diseases (TrVD: PAD with CVD and CHD) [1] [7] [15]. A number of risk factors for poorer outcomes have been identified in these patients, with polyvascular disease with Chronic Kidney Disease (CKD) and/or Diabetes Mellitus (DM) particularly markedly increasing the risk of cardiovascular events and/or heart failure [16] [17]. However, extremely long-term life expectancy, cardiovascular or cerebrovascular events, and the fate of the limb have not been confirmed in recent clinical follow-up data including causative risk factors in PAD patients. The purpose of the current study was to assess these outcomes for fifteen-year and causative risk factors with or without coexistent other vascular diseases in patients with PAD.

2. Patients and Methods

2.1. Patients

The subjects included Japanese patients with PAD who were hospitalized in Cardiovascular Hospital of Central Japan during the period from February 1, 2000 and April 30, 2020. This prospective cohort study complies with the principles of the Declaration of Helsinki, and the Medical Ethical Committee approved the study protocol in our hospital (CCJ-EA-006). Patients who gave their written informed consent to partake in this study were chosen as subjects. Patients satisfying the following inclusion criteria were selected: 1) an Ankle Brachial Pressure Index (ABI) of <0.90; 2) clinical symptoms (intermittent claudication or critical limb ischemia); 3) a stenotic lesion of ≥70% in iliac or femoropopliteal artery was specified with angiography or ultrasound. Patients with a treatment history of PAD including amputation of leg in another side were excluded from this study. The patients were also limited to those with PAD due to atherosclerosis. Patients with PAD due to non-atherosclerotic causes, such as vasculitis, Buerger disease, and fibromuscular dysplasia, were excluded. Patients with dementia were also excluded due to the difficulty of checking vital signs and obtaining other information.

2.2. Baseline Clinical Characteristics

Clinical data characteristics for each patient were obtained from the primary analysis for age, Body Mass Index (BMI), ABI, smoking history, hypertension, and Diabetes Mellitus (DM). The concentration of creatinine, albumin, triglyceride, total cholesterol, High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), glucose, D-dimer, and C-reactive protein (CRP) was determined with Hitachi 7180 automatic analyzer (Hitachi High-Tech Fielding Co., Tokyo, Japan). DM was defined as a fasting glucose level of >126 mg/dL at least two data or receiving antidiabetic treatment [18]. Hypertension was specified as blood pressure ≥140/90 mmHg recorded at least twice or a requirement for antihypertensive treatment. The estimated Glomerular Filtration Rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation with age and serum creatinine level [19].

2.3. Assessment of CVD and CHD

A brain Computed Tomography (CT) scan was performed in 5- or 10-mm thick sections without contrast agent (Aquilion 64, Toshiba, Tokyo, Japan). The scans were evaluated by two radiologists who were blinded to the statuses of the patients. Infarcts > 1.5 cm in diameter were defined to be cerebral infarction on brain CT. A low density lesion with a diameter ≤ 1.5 cm was defined as a lacunar infarction. Patients with CVD were defined as cerebral infarction and/or lacunar infarction on brain CT or a history of this disease. An electrocardiogram and an echocardiography were performed for each patient. CHD was defined as a documented history of ischemic heart disease (myocardial infarction, percutaneous

coronary intervention, composite of angina pectoris, or coronary artery bypass grafting) or a coronary angiogram (≥50% stenosis in at least one coronary artery).

2.4. Data Analysis and Endpoints

Each patient was followed up at 1, 3 and 4 months after treatment and assessed interval was 4- or 6-month. Vital signs and medical status were assessed with hospital data and written questionnaires for life statuses were assessed by the Foot Care Club [4] [20]. Ischemic strokes were determined as the presence of a new focal neurological deficit, and magnetic resonance imaging or CT was required to confirm the lesions. TIA was specified as the presence of a new neurological deficit lasting < 24 hours. Definition of myocardial infarction was signified previously [20] [21]. Peripheral restenosis during follow-up was determined as a decrease in ABI of ≥0.15% and ≥50% stenosis using angiography or duplex ultrasonography [20] [22], and major amputation was defined as above-the-ankle amputation.

The primary efficacy endpoints were Cardiovascular or Cerebrovascular Related Death (CCVD) and All-Cause Death (ACD). The secondary efficacy end-points were major adverse cardiovascular events (MACE: all-cause death, non-fatal myocardial infarction, non-fatal ischemic stroke, or transient ischemic attack) and cardiovascular and/or limb events (CVLE: CCVD, non-fatal myocardial infarction or cerebral infarction, transient ischemic attack, presence of a new peripheral lesion, repeat revascularization for a limb, or major amputation).

2.5. Statistical Analysis

All statistical analyses were calculated with IBM SPSS Statistics ver. 25.0 (IBM Corp, Armonk, NY). Categorical variables are signified as a number (%) and were compared by chi-square test with a Bonferroni correction. Continuous variables are expressed as a median (interquartile range) and were assessed by Kruskal-Wallis test with the Dann-Bonferroni method [23]. In multiple regression analysis, we calculated among all risk factors with simple Pearson correlations. Factors with $p < 0.05$ in this correlation analysis were calculated using stepwise forward multiple regression analysis to define relationships between the number of affected arteries and individual risk factors. We calculated Odds Ratio (OR) and Confidence Interval (CI) between DoVD or TrVD and risk factors with a univariate logistic analysis. Factors with $p < 0.05$ in these analyses were used in a multivariate logistic model to define the risk predictors for DoVD and TrVD. The Kaplan-Meier analysis was used to specify CCVD, ACD, MACE, and CVLE among PADa, DoVD, or TrVD and compared using the log-rank test with Bonferroni correction. In Cox univariate regression model, a Hazard Ratio (HR) and 95% CI were estimated for individual factors. Factors with $p < 0.05$ were used in multivariate regression models to define significant factors associated with these endpoints. A p-value < 0.05 was defined as statistically significant.

3. Results

3.1. Patient Characteristics and Causes of Death

Among 1053 patients, follow-up was possible for 1019 subjects. The mean and median follow-up periods were 80.2 ± 65.9 and 67 (29 - 115) months. The median and mean age were 72 (67 - 79) and 72.6 ± 9.9 years. The patients who died were 539 (52.9%) during the follow-up periods. The prevalence of CCVD was 50.5% (n = 272), as cardiac or major vascular disease (n = 193, 35.8%), cerebrovascular disease (n = 79, 14.7%). Other causes of deaths were malignancy (n = 108, 20.0%), pneumonia (n = 88, 16.3%), and other causes (n = 71, 13.2%). The cumulative 5-, 10-, and 15-year overall survival rates in all patients were 71.8%, 45.4%, and 32.7%, respectively. The baseline clinical characteristics and comorbidities in PAD patients with or without other vascular diseases are summarized in Table 1. Patients with PADa had higher ABI, serum albumin, eGFR, and HDL-C, and lower levels of CRP and D-dimer. The prevalences of CLI and DM were also lower in these patients.

3.2. Number of Affected arteries and Risk Factors

The number of affected arteries had significant positive correlations with age, men, CLI, LDL-C, and DM, and negative correlations with ABI, HDL-C, serum albumin, and eGFR in simple Pearson correlation analysis ($p < 0.05$). Stepwise forward multiple regression analysis of the relationship between the number of affected arteries and these factors was performed (Table 2). The number of affected arteries had significant negative correlations with eGFR, HDL-C, and ABI, and a positive correlation with DM ($p < 0.01$).

3.3. Risk Predictors for DoVD and TrVD

Relationships between risk factors and DoVD and TrVD were analyzed using multiple logistic analyses (Table 3). PAD with CVD was correlated with older age, lower ABI, eGFR, and atrial fibrillation; PAD with CHD showed a correlation with younger age, lower eGFR, HDL-C, higher LDL-C, and DM; and TrVD was correlated with lower ABI, eGFR, HDL-C, and DM.

3.4. Factors for ACD and CCVD

Cumulative incidence of the 5-, 10-, and 15-year rates for CCVD are demonstrated in Figure 1. There were significant differences among PADa, DoVD, or TrVD ($p < 0.001$, respectively). In Cox univariate analysis, age, CLI, CVD, CHD, hypertension, higher level of CRP, D-dimer, lower ABI, BMI, serum albumin, eGFR, and statin were associated to CCVD ($p < 0.05$). In multivariate analysis, higher age, CRP, lower serum albumin, eGFR, BMI, CLI, CVD, and CHD were also associated with CCVD, and statin also decreased CCVD (Table 4, $p < 0.05$).

The cumulative 5-, 10-, and 15-year incidence rates for ACD are demonstrated in Figure 2. There were significant differences between PADa and DoVD ($p < 0.001$) or TrVD ($p < 0.001$), but there was no significant difference between DoVD

and TrVD (p = 0.066). In Cox univariate analysis, age, CLI, CVD, DM, higher level of CRP, D-dimer, lower ABI, BMI, serum albumin, and eGFR were associated with ACD (p < 0.05). Treatment with statin or aspirin and revascularization were related to ACD. In multivariate analysis, higher age, CLI, CRP, lower BMI, serum albumin, eGFR, and CVD were also associated with ACD, and statin decreased ACD (Table 4, p < 0.05).

3.5. Factors for MACE and CVLE

The cumulative 5-, 10-, and 15-year incidence rates for MACE are shown in.

Table 1. Clinical characteristics and comorbidities in patients with Peripheral Arterial Disease (PAD) with or without other Vascular Disease (VD).

Factor	PAD alone n = 256 (25.1%)	Double VD n = 540 (53.0%)	Triple VD n = 223 (21.9%)
Age (year)	73 (65 - 79)	74 (67 - 80)	73 (67 - 79)
Gender (men)	177 (69.1%)	418 (77.4%)*	182 (81.6%)[§]
Ankle brachial pressure index	0.73 (0.56 - 0.88)	0.66 (0.51 - 0.80)*	0.67 (0.50 - 0.80)[§]
Body mass index (kg/m^2)	22.8 (20.0 - 25.1)	22.0 (20.0 - 24.2)	22.2 (20.0 - 24.3)
Critical limb ischemia	29 (11.3%)	106 (19.6%)*	44 (19.7%)[§]
Intermittent claudication	227 (88.7%)	434 (80.4%)*	179 (80.3%)[§]
Coronary heart disease	0	217 (40.2)	223 (100%)[¶]
Cerebral infarction	0	323 (59.8)	223 (100%)[¶]
Diabetes mellitus	85 (33.2%)	208 (38.5%)*	119 (53.4%)[§¶]
Hypertension	161 (62.9%)	372 (68.9%)	154 (69.1%)
Smoking	178 (69.8%)	407 (75.4%)	163 (73.1%)
Hemodialysis	17 (6.6%)	54 (10.0%)*	40 (17.9%)[§¶]
Atrial fibrillation	16 (6.3%)	70 (13.0%)*	23 (10.3%)
Basic metabolic panel			
eGFR (mL/min/1.73 m^2)	56.6 (51.9 - 73.2)	56.8 (42.5 - 69.4)*	50.6 (31.9 - 66.7)[§]
Albumin (g/dL)	4.1 (3.8 - 4.2)	4.0 (3.7 - 4.2)*	3.9 (3.7 - 4.2)[§]
D-dimer (µg/dL)	0.7 (0.5 - 1.4)	1.0 (0.5 - 2.2)*	1.1 (0.6 - 2.2)[§]
C-reactive protein (mg/dL)	0.14 (0.07 - 0.32)	0.18 (0.08 - 0.50)*	0.21 (0.10 - 0.54)[§]
Total cholesterol (mg/dL)	181 (152 - 214)	189 (160 - 215)	193 (171 - 223)[§]
Triglyceride (mg/dL)	125 (89 - 173)	129 (87 - 203)	128 (95 - 179)
HDL-C (mg/dL)	52 (42 - 62)	47 (40 - 58)*	46 (36 - 54)[§]
LDL-C (mg/dL)	111 (90 - 128)	114 (90 - 135)	117 (97 - 137)
Medications			
Thienopyridines	102 (39.8%)	276 (51.1%)*	135 (60.5%)[§¶]
Aspirin	168 (65.6%)	393 (72.9%)	184 (82.5%)[§]
Beraprost	103 (40.2%)	205 (38.0%)	70 (31.4%)
Cilostazol	60 (23.4%)	162 (30.0%)	48 (21.5%)[¶]

Continued

Ca antagonist	134 (52.3%)	289 (53.5%)	115 (51.6%)
ACE inhibitor	26 (10.2%)	56 (10.4%)	26 (11.7%)
ARB	65 (25.4%)	165 (30.6%)	85 (38.1%)[§]
β-blocker	24 (9.4%)	88 (16.3%)	50 (22.4%)[§¶]
Statin	156 (60.9%)	339 (62.8%)	153 (68.6%)
Revascularization	143 (55.9%)	324 (60.0%)	143 (64.4%)

Double VD: PAD with cerebral infarction or coronary heart disease; Triple VD: PAD with cerebral infarction and coronary heart disease; eGFR: estimated glomerular filtration rate; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker. *: $p < 0.05$ (PAD alone vs. Double VD); §: $p < 0.05$ (PAD alone vs. Triple VD); ¶: $p < 0.05$ (Double VD vs. Triple VD).

Table 2. Correlations between the number of affected arteries and other risk factors in stepwise forward multiple regression analysis.

Risk factor	β	B	95% C.I.	P-value
eGFR (mL/min/1.73 m^2)	−0.134	−0.004	−0.006 to −0.002	<0.001
Diabetes mellitus	0.127	0.176	0.083 to 0.270	<0.001
HDL-C (mg/dL)	−0.115	−0.005	−0.008 to −0.002	0.001
ABI	−0.104	−0.255	−0.418 to −0.093	0.002

$R^2 = 0.059$; F for change in $R^2 = 0.009$; $P = 0.006$. β: standardized coefficient; B: non-standardized coefficient; CI: confidence interval for B; eGFR: estimated glomerular filtration rate; ABI: ankle brachial pressure index.

Table 3. Relationships between three arterial lesion levels and risk factors in multiple logistic analysis.

	Double vascular diseases						Triple vascular diseases		
Risk factor	PAD and CVD (n = 323)			PAD and CHD (n = 217)			PAD, CVD, and CHD (n = 223)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age (year)	1.018	1.001 - 1.037	0.048	0.976	0.955 - 0.998	0.030			
ABI	0.353	0.181 - 0.691	0.002				0.419	0.184 - 0.953	0.038
Diabetes mellitus				1.598	1.040 - 2.456	0.032	2.332	1.516 - 3.626	<0.001
eGFR (mL/min/1.73 m^2)	0.992	0.986 - 0.990	0.007	0.990	0.980 - 0.999	0.034	0.982	0.972 - 0.992	<0.001
HDL-C (mg/dL)				0.978	0.964 - 0.993	0.004	0.979	0.964 - 0.994	0.005
LDL-C (mg/dL)				1.005	1.001 - 1.010	0.017			
Atrial fibrillation	1.973	1.046 - 3.724	0.036						

PAD: peripheral arterial disease; CVD: cerebrovascular disease; CHD: coronary heart disease; OR: odds ratio; CI: confidence interval; ABI: ankle brachial pressure index; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol.
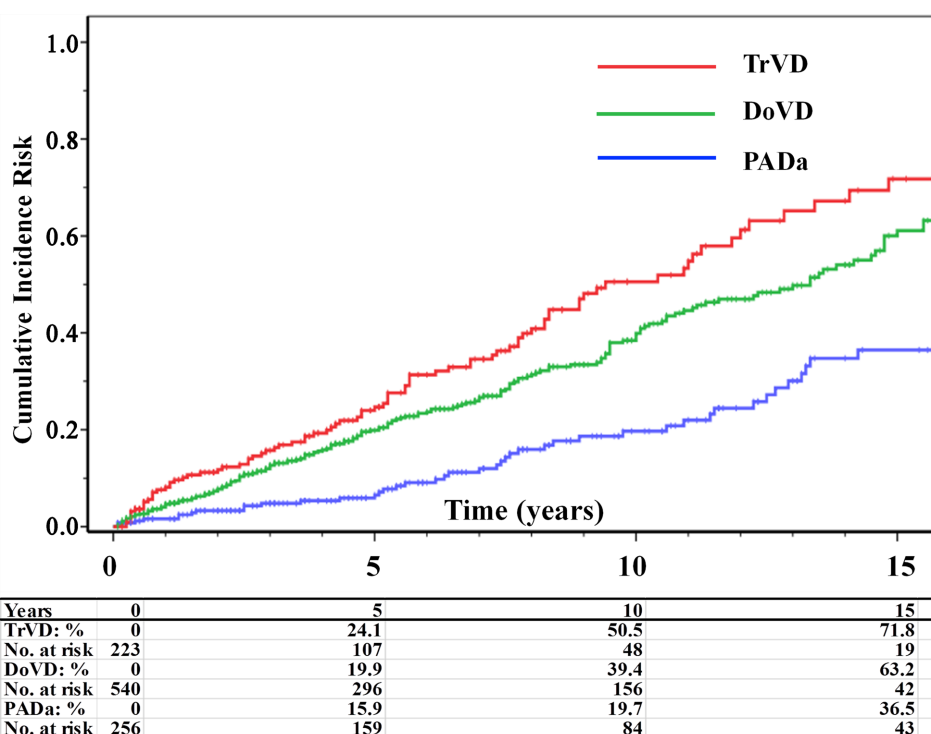
Figure 1. Cumulative 5-, 10-, and 15-year incidence rates for cardiovascular or cerebrovascular related death (CCVD) are demonstrated with significant differences among PAD alone (PADa), double vascular diseases (DoVD: PAD with CVD or CHD), or triple vascular diseases (TrVD: PAD with CVD and CHD) (all p < 0.001).
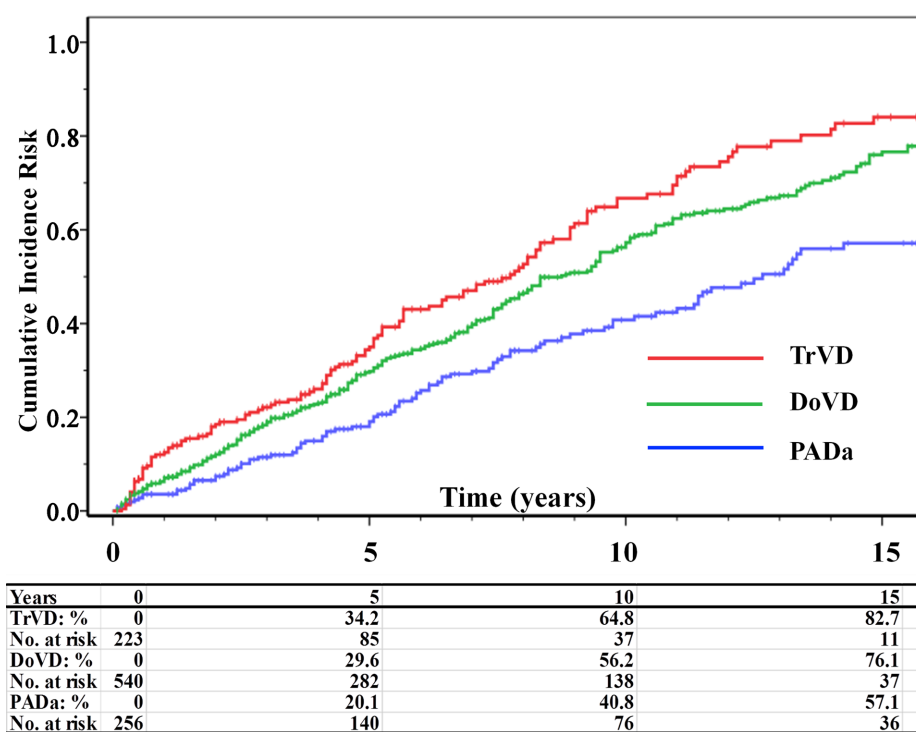

Figure 2. Cumulative 5-, 10-, and 15-year incidence rates for all-cause death (ACD) in PAD alone (PADa), double vascular diseases (DoVD: PAD with CVD or CHD) or triple vascular diseases (TrVD: PAD with CVD and CHD). There were significant differences between PADa and DoVD (p < 0.001) or TrVD (p < 0.001), but there was no significant difference between DoVD and TrVD (p = 0.066).

Table 4. Cox multivariate regression analysis for Cardiovascular or Cerebrovascular Related Death (CCVD) and All-Cause Death (ACD).

Factor	CCVD			ACD		
	Multivariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (year)	1.051	1.036 - 1.067	<0.001	1.054	1.042 - 1.066	<0.001
Body mass index (kg/m²)	0.955	0.916 - 0.996	0.030	0.949	0.919 - 0.981	0.002
Critical limb ischemia	1.939	1.375 - 2.732	<0.001	1.609	1.223 - 2.117	0.001
Cerebral infarction	1.666	1.230 - 2.255	0.001	1.338	1.068 - 1.676	0.011
Coronary heart disease	1.477	1.119 - 1.949	0.006	1.184	0.951 - 1.474	0.131
Serum albumin (g/dL)	0.587	0.418 - 0.823	0.002	0.521	0.400 - 0.678	<0.001
eGFR (mL/min/1.73 m²)	0.984	0.978 - 0.991	<0.001	0.987	0.982 - 0.992	<0.001
C-reactive protein (mg/dL)	1.110	1.016 - 1.213	0.021	1.128	1.055 - 1.207	<0.001
Statin	0.487	0.355 - 0.667	<0.001	0.469	0.368 - 0.598	<0.001

HR: hazard ratio; CI: confidence interval; eGFR: estimated glomerular filtration rate.

Figure 3. There were significant differences among PADa, DoVD, or TrVD (p < 0.001, respectively). In Cox univariate analysis, age, men, CLI, CVD, CHD, DM, higher level of CRP, D-dimer, lower BMI, ABI, serum albumin, eGFR, and statin were associated to MACE (p < 0.05). In multivariate analysis, higher age, CRP, lower serum albumin, eGFR, CLI, CHD, and DM were also associated with MACE, and statin decreased MACE (**Table 5**, p < 0.05).

The cumulative 5-, 10-, and 15-year incidence rates for CVLE are shown in **Figure 4**. There were significant differences among PADa, DoVD, or TrVD
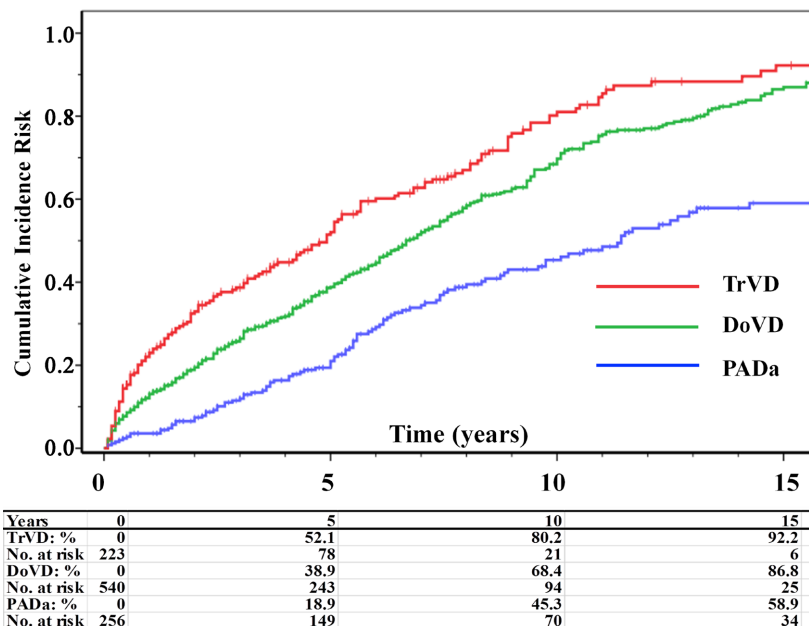

Years	0	5	10	15
TrVD: %	0	52.1	80.2	92.2
No. at risk	223	78	21	6
DoVD: %	0	38.9	68.4	86.8
No. at risk	540	243	94	25
PADa: %	0	18.9	45.3	58.9
No. at risk	256	149	70	34

Figure 3. Cumulative 5-, 10-, and 15-year incidence rates for major adverse cardiovascular events (MACE) with significant differences among PAD alone (PADa), double vascular diseases (DoVD: PAD with CVD or CHD), or triple vascular diseases (TrVD: PAD with CVD and CHD) (all p < 0.001).
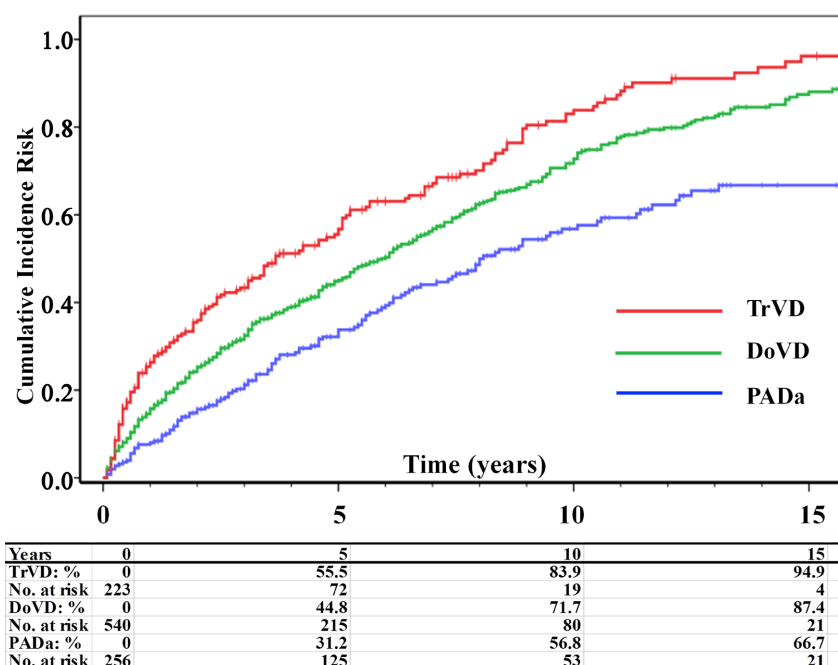
Figure 4. Cumulative 5-, 10-, and 15-year incidence rates for cardiovascular and/or limb events (CVLE) with significant differences among PAD alone (PADa), double vascular diseases (DoVD: PAD with CVD or CHD), or triple vascular diseases (TrVD: PAD with CVD and CHD) (all p < 0.001).

Table 5. Cox multivariate regression analysis for Major Adverse Cardiovascular Events (MACE) and Cardiovascular and/or Limb Events (CVLE).

Factor	MACE Multivariate analysis			CVLE Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (year)	1.038	1.028 - 1.049	<0.001	1.022	1.012 - 1.032	<0.001
ABI	0.705	0.491 - 1.014	0.059	0.663	0.469 - 0.936	0.020
Critical limb ischemia	1.447	1.125 - 1.862	0.004	1.313	1.012 - 1.702	0.040
Coronary heart disease	1.841	1.514 - 2.238	<0.001	1.510	1.245 - 1.830	<0.001
Diabetes mellitus	1.328	1.091 - 1.617	0.005	1.331	1.066 - 1.672	0.012
Serum albumin (g/dL)	0.655	0.519 - 0.826	<0.001	0.717	0.571 - 0.900	0.004
eGFR (mL/min/1.73 m^2)	0.994	0.990 - 0.999	0.011	0.993	0.989 - 0.997	0.001
C-reactive protein (mg/dL)	1.114	1.048 - 1.185	0.001	1.070	1.005 - 1.139	0.035
Statin	0.440	0.356 - 0.543	<0.001	0.474	0.387 - 0.580	<0.001

HR: hazard ratio, CI: confidence interval, ABI: ankle brachial pressure index, eGFR: estimated glomerular filtration rate.

(p < 0.001, respectively). In Cox univariate analysis, age, men, CLI, CVD, CHD, DM, higher level of CRP, D-dimer, lower BMI, ABI, serum albumin, eGFR, and statin were associated to CVLE (p < 0.05). In multivariate analysis, higher age, CRP, lower ABI, serum albumin, eGFR, CLI, CHD, and DM were also associated with CVLE, and statin also decreased CVLE (Table 5, p < 0.05).

4. Discussion

This study assessed the first clinical evidence for fifteen-year mortality, cardiovascular or cerebrovascular events, and fate of the limb in PAD patients with or without polyvascular disease. When compared with PADa, patients with DoVD or TrVD had significantly higher rates of CCVD and ACD during the follow-up period. We found that the number of affected arteries had significant correlations with CCVD, MACE, and CVLE, and the risk of cardiovascular events increased in a stepwise manner with each additional arterial bed. Furthermore, lower eGFR, ABI, and DM showed close relationships with the number of affected vascular territories and increased severity of vascular atherosclerosis.

The definition of coinstantaneous lesions of atherosclerotic disease in different vascular territories depends on the methods and criteria used for diagnosis. In particular, the criteria and definition for CVD and CHD are particularly dominan for diagnosis of DoVD or TrVD in polyvascular disease, and there is a risk of under diagnosis. Thus, we used severe threshold levels in the definitions for CVD and CHD in this study. Multiple comparisons among the three groups were difficult, but these analyses were instrumental in identifying risk factors and outcomes of polyvascular disease in patients with PAD.

We found several important differences between DoVD and TrVD. Within DoVD, there were some differences in the risk factor between CVD and CHD in multiple logistic analysis. The patient age as a risk factor was older in CVD and younger in CHD. In REACH Registry [6], the mean ages in these three arterial diseases were youngest in CHD, middle in CVD, and oldest in PAD. These basic characteristics may affect the differences of overlap between CVD and CHD in patients with PAD. Atrial fibrillation was an independent predictor for CVD. The patients with atrial fibrillation have an average annual risk of CVD of approximately 5% [24]. Whereas, CHD was correlated with lower HDL-C, higher LDL-C, and DM. CHD is closely related lipid abnormality [25].

The prevalence of CCVD was 50.5% in ACD. CCVD was also strongly correlated with higher age, CRP, lower serum albumin, eGFR, BMI, CLI, CVD, and CHD. Together with higher age and CRP, DM is considered one of the strongest risk factors for PAD, CVD, and CHD [2] [11] [26]. Of importance, DM is particularly strongly associated with the severe stage in PAD as CLI [2] [26]. Furthermore, CVD was also an independent predictor for ACD. Severe systemic atherosclerosis reflected by CVD is responsible for ACD or CCVD [11].

Lower eGFR was an independent risk factor throughout DoVD and TrVD. Several studies have documented that lower eGFR is a prognostic indicator of CCVD [27] [28]. Moreover, we have also demonstrated lower BMI and geriatric nutritional risk index are significant predictive factors for ACD, CCVD, and CVLE in patients with PAD [4] [29]. The incidence of MACE or CVLE significantly increased with the number of arterial beds. Especially, CLI, lower eGFR, serum albumin, and higher CRP were significant risk factors for all outcomes. CLI and lower ABI are related to a higher risk of MACE and CVLE based on severe systemic

atherosclerosis [4] [30]. These results documented that patient with chronic kidney disease, malnutrition, or severe PAD have systemic atherosclerosis as polyvascular disease which is the cause of morbidity or mortality.

Higher LDL-C had a significant correlation with CHD, and lower HDL-C were significantly associated with CHD and TrVD. Lipid abnormality is an independent risk factor for patients with polyvascular disease, and intensive lipid-lowering therapy is effective for decreasing vascular events in these patients [1] [31]. Statins improve cardiovascular events and have an antiatherogenic effect on CHD [32]. Statin therapy is also effective for decreasing ACD and MACE in symptomatic and asymptomatic patients with PAD [33] [34]. These results suggest that statins also improve the long-term clinical risks for CCVD and CVLE.

5. Limitations of the Study

There are several limitations that should be considered in his study. First, the number of patients recruited to this study was relatively small. Second, the study was based on the data from a single facility. Third, the prescription rate of statins was relatively lower comparing to recent guidelines at the time of treatment, but the prevalence has increased over time. These results require further prospective long-term clinical follow-up data for these outcomes and risk factors in a larger cohort with PAD.

6. Conclusion

Polyvascular disease was independently associated with increased fifteen-year mortality, cardiovascular events, and the fate of the limb with diverse risk factors in PAD patients. The number of affected arteries had significant correlations with CCVD, ACD, MACE, and CVLE in patients with PAD.

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Conflicts of Interest

The authors declare no conflicts of interest.

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