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What are the Predictors of Death in Patients With Cranio-Cervical Artery Dissection?

Kraniyo-Servikal Arter Diseksiyonlu Hastalarda Ölümün Belirleyicileri Nelerdir?

Yüksel KAPLAN, Özden KAMIŞLI, Sibel ALTINAYAR, Cemal ÖZCAN

Department of Neurology, İnönü University Faculty of Medicine, Malatya, Turkey

ABSTRACT

Introduction: Few studies have reported the predictive factors related to mortality in patients with cranio-cervical artery dissections (CCAD). Our aim was to investigate the predictors related to in-hospital mortality in patients with CCAD and its subgroups.

Methods: Sixty-seven patients diagnosed with carotid artery dissection (CAD) or vertebral artery dissection (VAD), admitted to our clinic between 2000 and 2013, were retrospectively reviewed. Age, gender, modified Rankin Scale scores (pre-stroke and at admission), clinical presentation type, location of the dissection, risk factors, and treatments were analyzed as mortality-related prognostic factors. Of the 67 patients, 12 (17.9%) died, five (7.46%) with CAD and seven (10.44%) with VAD. We compared the prognostic characteristics of the surviving versus deceased patients with CCAD and in the subgroups with CAD and VAD.

Results: Age above 45 years, severe disability at admission, presentation with stroke, and intracranial VAD occurred more frequently in deceased patients and were independent variables related to mortality in patients with CCAD and its subgroup with VAD. Severe disability at admission alone was related to mortality in patients with CAD. Hypertension and hypercholesterolemia were independent variables related to mortality in patients with CCAD.

Conclusion: Severe disability at admission was a mortality predictor in both CAD and VAD. Although the initial severity of stroke is reportedly related to poor outcomes in patients with CCAD, it has not previously been directly identified as a predictor of mortality in patients with CAD or VAD.

Keywords: Cranio-cervical artery dissection, carotid artery dissection, vertebral artery dissection, mortality, predictor

ÖZET

Amaç: Kraniyo-servikal arter diseksiyonlu (KSAD) hastalarda ölümle ilişkili belirleyici faktörler az sayıdaki çalışmada bildirilmiştir. Bu çalışmada amacımız, KSAD ve alt tiplerinde hastane içi ölümle ilişkili belirleyici faktörleri araştırmaktır.

Yöntem: 2000-2013 tarihleri arasında kliniğimizde karotis arter diseksiyonu (KAD) veya vertebral arter diseksiyonu (VAD) tanısı alan 67 hasta retrospektif olarak gözden geçirildi. Yaş, cinsiyet, inme öncesi ve hastaneye yatış sırasında saptanan modifiye Rankin skoru, diseksiyonun klinik prezentasyonu, diseksiyonun lokalizasyonu, risk faktörleri ve tedaviler mortaliteyle ilişkili prognostik faktörler olarak değerlendirildi. Altmış yedi hastanın 12'si (%17,9) ölmüştü. Ölen hastaların 5'inde (%7,46) KAD, 7'sinde (%10,44) VAD vardı. KSAD ve alt grupları olan KAD ve VAD'lı yaşayan ve ölen hastalar prognostik karakteristikler yönünden karşılaştırıldı.

Bulgular: KSAD'lı ve bir alt grubu olan VAD'lı ölen hastalarda; 45 yaşın üstünde olmak, hastaneye yatış sırasındaki özürlülük, diseksiyonun inme ile prezentasyonu, diseksiyonun intrakranyal vertebral arterde olmasının mortaliteyle ilişkili bağımsız risk faktörleri olduğu saptandı. KAD'da ise sadece hastaneye yatış sırasındaki özürlülük mortaliteyle ilişkili bağımsız risk faktörüydü. Hipertansiyon ve hiperkolesterolemi, KSAD'lu hastalarda mortaliteyle ilişkili faktörlerdi.

Sonuç: Hem KAD hem de VAD'lı hastalarda yatış sırasındaki özürlülük, mortalite için belirleyici bir faktördü. KSAD'lı hastalarda inmenin başlangıçtaki ağırlığının kötü prognozla ilişkili olduğu bildirilmiş olmasına rağmen, KAD veya VAD'lı hastalarda doğrudan mortalite ile ilişkili olduğu tanımlanmamıştır.

Anahtar kelimeler: Kraniyo-servikal arter diseksiyonu, karotis arter diseksiyonu, vertebral arter diseksiyonu, ölüm, belirleyici

INTRODUCTION

The estimated annual incidence of cranio-cervical artery dissection (CCAD) is reported as five cases per 100,000 in the general population (1). Because some dissections are asymptomatic or cause only minor symptoms, the true incidence may be higher than those reported (2).

Intimal tears, intramural hematomas, and dissecting aneurysms can spontaneously occur or as a result of trauma (1,2,3). Spontaneous CCAD is the cause of up to one in four strokes in young and middle-aged patients (1). The prognosis varies, and the dissection can range from being asymptomatic to causing profound neurological deficits and death (3). The annual incidence of carotid artery dissection (CAD) is estimated to be 2.5-3 per 100,000 (4). Patients with CAD tend to have a good outcome, with a mortality rate of <5% (2,3). However, vertebral artery dissection (VAD) is an uncommon and potentially devastating condition with an estimated annual incidence

Correspondence Address/Yazışma Adresi: Dr. Yüksel Kaplan, Department of Neurology, İnönü University Faculty of Medicine, Malatya, Turkey Phone: +90 532 468 71 69 E-mail: yukselkablan@yahoo.com

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of 1-1.5 per 100.000 (5). Some authors have reported that VAD is more frequent and has a relatively good prognosis with an estimated mortality rate varying from 2% to 46% (6,7,8).

The extent of the initial cerebral ischemia, initial severity of the stroke, arterial occlusion, and diffusion restriction abnormalities have been reported to be associated with poor outcomes in patients with CAD (3,4,9,10). The initial severity of stroke, bilateral dissections, intracranial dissection, presentation of the dissection with subarachnoid hemorrhage (SAH), and recurrent bleeding have been associated with poor outcomes in patients with VAD (6,7,8,11,12,13). Moreover, ruptured intracranial dissection, presentation of the dissection with SAH, and recurrent bleeding have been reported to be related to mortality in patients with VAD (6,7,13).

Despite the results reported by previous studies regarding CAD or VAD on poor patient outcomes, there are only a few studies providing information regarding predictive factors related to mortality in these patients.

The aim of this study was to identify factors associated with in-hospital mortality and potential predictive factors related to mortality in patients with CCAD and its subgroups, CAD and VAD.

METHODS

Study Design

We retrospectively collected data for all patients presenting with dissection of the internal carotid or vertebral artery from January 2000 to January 2013. All patients were admitted to our institution and were later examined in the neurology clinic or died in the neurology department, including the neurology ward and intensive care unit. Data were collected from the outpatient clinic and hospital medical records. At our institution, patient data were recorded in medical records between 1990 and 2006 and thereafter, in computerized databases systems. An archive search was performed for patients admitted prior to 2006, and the computerized database system was reviewed for patients admitted after 2006.

Diagnoses and Investigations

All patients had undergone Doppler sonography of the carotid and/or vertebral arteries. Additional neuroradiological investigations were performed in all patients. VAD and CAD were both clinically and angiographically diagnosed; the medical records and neuroimaging studies of these patients were re-evaluated by the present study team. Dissections were identified based on the characteristic neuro-radiological findings, clinical presentation, and the absence of atherosclerotic disease elsewhere in the cerebrovascular circulation (14). Final diagnosis was based on one of the clinical findings, including stroke, transient ischemic attack, or purely local signs, in combination with at least one confirming angiographic sign. Patients with clinically diagnosed CAD or VAD confirmed by digital subtraction angiography (DSA), magnetic resonance angiography (MRA) and/or magnetic resonance imaging (MRI), or CT angiography (CTA) were included. Radiological diagnoses of the dissections were based on classic angiographic signs: mural hematoma, irregular stenosis (string sign), double lumen, and intimal flaps. Patients with typical clinical findings but without radiological confirmation were excluded.

Atheromatous plaques, which are associated with severe intimal diseases, can mimic the neuroimaging finding of dissection in elderly patients (14). Special care was taken to examine the neuroimaging findings in such patients. Patients with a confirmed diagnosis of CAD or VAD were included in the study.

The following clinical variables were recorded: age, gender, modified Rankin Scale (mRS) scores (15) (pre-stroke and at the time of admission), clinical presentation, location of the dissection, and characteristics of dissection, vascular, and other risk factors known to be associated with artery dissections, type of treatment received, length of hospital stay, death, and cause of death.

Assessment of Variables

Pre-stroke disabilities were assessed according to medical histories and were assigned a mRS score. The severity of clinical symptoms at the time of admission was assessed by neurological examination at hospital admission and was scored with mRS. In this evaluation, consciousness level (alert, somnolent, stupor, or coma), deficits in motor function (no dysfunction or mono-, hemi-, or tetraparesis), and the presence or absence of speech disturbances were considered.

Patients were classified into two groups based on the mRS scores: scores of 0-2 were considered favorable with a functional independence and scores of 3-5 were considered poor with a functional impairment necessitating assistance. Death was coded as mRS 6.

On admission, clinical presentation was defined according to the duration of ischemic deficits as stroke (>24 h), transient ischemic attack (<24 h), or purely local signs, including head, facial, or neck pain, tinnitus, and Horner's syndrome. The localizations of the dissections were classified as CAD or VAD and then categorized into four subgroups: intracranial CAD, extracranial CAD, intracranial VAD, and extracranial VAD.

The nature of the dissections was assessed as spontaneous or associated with minor trauma. For exclusion criteria, a history of major neck or head trauma, such as car accident or sports trauma causing blunt arterial injury, and whether the trauma prompted a visit to a physician or hospitalization were considered.

The following vascular risk factors were evaluated: hypertension (HT), hypercholesterolemia (HC), diabetes mellitus (DM), and a history of regular smoking at the time of the event. HT was defined as the past use of anti-hypertensive treatment or blood pressure >140/90 mmHg diagnosed as HT during follow-up in the hospital. DM was defined as the use of insulin or oral antidiabetic treatment or a fasting glucose level >126 mg/dL and/or a hemoglobin A1c level >6.5% during follow-up, as determined by a treating physician. HC was defined as a fasting total cholesterol level >220 mg/dL and/or the use of lipid-lowering treatment.

Other risk factors known to be associated with artery dissections were screened as follows: use of oral contraceptives or postmenopausal hormone replacement therapy at the time of the event, migraine, hyperhomocysteinemia, fibromuscular dysplasia (if detected during digital subtraction angiography procedures), and a history of connective tissue disorders. These factors were accepted as pre-existing conditions when included in medical history or diagnosed during follow-up.

The type of treatment received was categorized as follows: (1) intravenous heparin followed by oral warfarin with a target international ratio (INR) of 2.5 (2.0-3.0) or oral acetylsalicylic acid (100-300 mg/day), (2) subcutaneous low molecular-weight heparin followed by oral warfarin with a target INR of 2.5 (2.0-3.0) or oral acetylsalicylic acid (100-300 mg/day), (3) acetylsalicylic acid (100-300 mg/day) alone, and (4) thrombolytic treatment.

Table 1. Comparison of demographic and clinical characteristics between surviving and deceased patients with cranio-cervical dissection

Variable		All patients (n=67) n (%)	Surviving patients (n=55) n (%)	Deceased patients (n=12) n (%)	p value
Age (mean±SD, year) (min-max)		59.45±15.53 (26-86)	56.71±15.11 (26-82)	72±10.81 (46-86)	0.001
Gender (female/male)		20/47	17/38	3/9	1.000
Pre-stroke disability	mRS score 0-2	66 (98.5)	54 (98.2)	12 (100)	1.000
	mRS score 3-5	1 (1.5)	1 (1.8)	0 (0)	
Disability at admission	mRS score 0-2	47 (70.1)	44 (80)	3 (25)	0.0001
	mRS score 3-5	20 (29.9)	11 (20)	9 (75)	
Clinical presentation	Stroke	33 (49.3)	23 (41.8)	10 (83.3)	0.009
	TIA	8 (11.9)	7 (12.7)	1 (8.3)	1.000
	Local signs only	26 (38.8)	25 (45.5)	1 (8.3)	0.021
Location of dissection	Carotid artery	28 (41.8)	23 (41.8)	5 (41.7)	0.992
	Vertebral artery	39 (58.2)	32 (56.2)	7 (58.3)	
Subgroup of dissection	Carotid artery-extracranial	24 (35.8)	20 (36.4)	4 (33.3)	0.954
	Carotid artery-intracranial	4 (6)	3 (5.5)	1 (8.3)	1.000
	Vertebral artery-extracranial	32 (47.8)	30 (54.5)	2 (16.7)	0.017
	Vertebral artery-intracranial	7 (10.4)	2 (3.6)	5 (41.7)	0.001
Nature of dissection	Spontaneous	56 (83.6)	46 (83.6)	10 (83.3)	1.000
	Minor trauma	11 (16.4)	9 (16.4)	2 (16.7)	
Hypertension		37 (56.1)	27 (50)	10 (83.3)	0.035
Diabetes mellitus		18 (26.9)	15 (27.3)	3 (25)	1.000
Hypercholesterolemia		40 (59.7)	29 (52.7)	11 (91.7)	0.02
Regular cigarette smoking		20 (29.8)	17 (30.9)	3 (25)	1.000
Other risk factors	Yes	20 (29.9)	16 (29.1)	4 (33.3)	0.741
	No	47 (70.1)	39 (70.9)	8 (66.7)	
Treatment	IV heparin + warfarin	42 (62.7)	34 (61.8)	8 (66.7)	0.950
	IV heparin + ASA	0	0	0	
	ASA	17 (25.4)	14 (25.5)	3 (25)	
	LMWH + warfarin	5 (7.5)	4 (7.3)	1 (8.3)	
	LMWH + ASA	2 (3)	2 (3.6)	0	
	IV thrombolysis	1 (1.5)	1 (1.8)	0	
Duration of hospital stay (mean±SD, day) (min-max)		15.39±10.46 (1-64)	14.47±9.57 (1-64)	19.58±13.55 (6-54)	0.239

Data are presented as n (%), except age, gender, and hospital stay. SD: standard deviation; TIA: transient ischemic attack; mRS: modified Rankin scale; IV: intravenous; ASA: acetylsalicylic acid; LMWH: low molecular-weight heparin

Mortality causes were categorized as neurological for deaths related to stroke severity or stroke complications and as systemic for deaths due to any systemic complications during clinical follow-up.

In the initial evaluation, patients with CCAD were divided into two groups, surviving and deceased patients, and risk variables were compared between the groups. In the second evaluation, both surviving and deceased patients were divided into four groups depending on the location of the dissection: surviving patients with CAD, deceased patients with CAD, surviving patients with VAD, and deceased patients with VAD. The risk variables were compared between the surviving and deceased subgroups in each category.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS, version 13; SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous variables are presented as means±standard deviation. Categorical variables are presented as numbers and percentages.

Normality for continuous variables was determined using the Shapiro-Wilk test. Based on the test result, continuous variables were compared using an unpaired t-test and the Mann-Whitney U test. Fisher's exact test and Pearson's chi-squared test were used to compare categorical variables. Univariate and multivariate logistic regression analyses were performed to identify associations between variables and mor-

Table 2. Predictors of deceased patients with cranio-cervical dissection

Variable	Odds ratio (95% CI)	p value
Age		
(0) ≤45 years	1.48 (1.23-1.78)	0.027
(1) >45 years		
Disability at admission		
(0) mRS score 0-2	3.75 (2.01-6.9)	0.0001
(1) mRS score 3-5		
Clinical presentation		
(0) Local signs	1.99 (1.33-2.97)	0.009
(1) Stroke		
(0) Vertebral artery-extracranial	11.45 (2.51-52.1)	0.001
(1) Vertebral artery-intracranial		
(1) Hypertension	1.66 (1.15-2.40)	0.035
(1) Hypercholesterolemia	1.73 (1.28-2.35)	0.020

(1), risk factor; (0), not a risk factor. mRS: modified Rankin scale; 95% CI, 95% confidence interval

tality in patients with CAD or VAD. Values of $p<0.05$ were considered statistically significant.

RESULTS

Sixty-seven patients with CCAD (male/female, 47/20; mean age, 59.45±15.53 years; range, 26-86) were included in the study.

Neuro-Imaging Studies

A CCAD diagnosis was established using DSA in 42 (62.6%) patients, MRA and DSA in nine (13.4%), CTA and/or MRA in 14 (21%), and MRA by T1-weighted MRI with fat suppression in two (3%). Furthermore, all patients underwent cranial CT and/or MRI.

Patients with CCAD were divided into two groups: surviving and deceased patients. Clinical follow-up revealed that 12 (17.9%) patients died, with 83.3% from neurological causes and 16.7% because of systemic complications. Consequently, the groups of surviving and deceased patients comprised 55 and 12 patients, respectively.

Clinical and Demographic Characteristics of Patients with CCAD

Based on clinical follow-up data, 12 (17.9%) of the 67 patients died: five (7.5%) had CAD and seven (10.4%) had VAD. The deceased patients were significantly older than the surviving patients ($p<0.05$). Compared with the surviving patients, the deceased patients had a significantly higher incidence of mRS scores of 3-5 at the time of admission ($p<0.05$).

The major presentation of dissections significantly differed between the two groups ($p<0.05$), with stroke being the major presentation in deceased patients and local symptoms being the major presentation in surviving patients.

The location of dissections also significantly differed ($p<0.05$) between the groups: the major location in the deceased patients was intracranial VAD and in the surviving patients extracranial VAD.

The frequencies of HT and HC were significantly higher in deceased patients with CCAD ($p<0.05$). A comparison of demographic and clinical characteristics between surviving and deceased patients with CCAD is presented in Table 1. Based on multivariate regression analysis, age above 45 years, mRS scores of 3-5 at admission, presentation of dissection as stroke, presence of HT and HC, and dissection in the intracranial vertebral artery were significantly related to in-hospital mortality in patients with CCAD (Table 2).

Comparison of Demographic and Clinical Characteristics in Patients with CAD

Of the 67 patients diagnosed with CCAD, 28 (41.8%) had CAD, five (17.9%) of whom died. Only severe disability at admission (mRS score 3-5) was significantly more common in deceased patients with CAD than that in surviving patients with CAD (Table 3).

Comparison of Demographic and Clinical Characteristics in Patients with VAD

Of the 67 patients diagnosed as having CCAD, 39 (58.2%) had VAD, seven (17.9%) of whom died. High patient age, severe disability at admission (mRS score 3-5), presentation of dissection as stroke, and dissection in the intracranial vertebral artery were significantly more frequent in deceased patients with VAD than in surviving patients with VAD (Table 4). Based on multivariate regression analysis, age above 45 years, severe disability at admission (mRS score 3-5), presentation of dissection as stroke, and dissection in the intracranial vertebral artery were significantly related to in-hospital mortality in patients with VAD (Table 5).

Comparison of the Type of Treatment Received

The type of treatment received did not significantly differ in surviving and deceased patients with CCAD or its groups ($p>0.05$; Table 5).

DISCUSSION

In this study, we investigated the in-hospital mortality and potentially predictive factors related to mortality in patients with CCAD and its subtypes. Age above 45 years, severe disability at admission, presentation of the dissection as stroke, and dissection in the intracranial vertebral artery occurred more frequently in patients with both CCAD and VAD and were independent mortality predictors in these patients. Severe disability at admission alone was related to mortality in patients with CAD. HT and HC were independent factors for mortality in patients with CCAD. However, there was no significant difference in the frequency of HT or HC between CAD and VAD.

The increased CCAD diagnosis over the last two decades can be attributed to an increased awareness of the clinical manifestations of dissections and to the increased use of non invasive diagnostic imaging techniques (1). Nevertheless, few studies have examined predictive factors related to mortality in CCAD patients. In the present study, the rates of in-hospital mortality were 17.9% in patients with CCAD: 7.46% in patients with CAD and 10.44% in patients with VAD.

Dziewas et al. (4) reported a 13% rate of death or severe handicap (mRS score 4 or 5) in a study that included 126 patients with CCAD. In that study, one (1%) patient died and a poor outcome was found in 15% of patients with CAD and 9% of patients with VAD. However, their study was retrospectively performed, and the outcomes were evaluated after a maximum of 6 months; data for in-hospital or short-term mortality were not included. Mortality rates of 2%-46% have been estimated in patients with VAD, and rates of <5% have been reported in patients with CAD (3,7,8). In the present study, the mortality rate in patients with VAD was consistent with these previous rates; however, the mortality rate in patients with CAD was higher than that previously reported.

Table 3. Comparison of demographic and clinical characteristics between surviving and deceased patients with carotid artery dissection

Variable		Surviving-CAD (n=23) n (%)	Deceased-CAD (n=5) n (%)	p value
Age (mean±SD, year) (min-max)		58.83±17.25 (26-82)	74.4±9.20 (64-86)	0.059
Gender (female/male)		7/16	2/3	1.000
Pre-stroke disability	mRS score 0-2	22 (95.7)	5 (100)	1.000
	mRS score 3-5	1 (4.3)	0 (0)	
Disability at admission	mRS score 0-2	15 (65.2)	0 (0)	0.013
	mRS score 3-5	8 (34.8)	5 (100)	
Clinical presentation	Stroke	8 (34.8)	3 (60)	0.353
	TIA	3 (13)	1 (20)	1.000
	Local signs only	12 (52.2)	1 (20)	0.333
Subgroup of dissection	Carotid artery-extracranial	20 (86.9)	4 (80)	0.459
	Carotid artery-intracranial	3 (13.1)	1 (25)	1.000
Nature of dissection	Spontaneous	21 (91.3)	5 (100)	1.000
	Minor trauma	2 (8.7)	0 (0)	
Hypertension		13 (56.5)	4 (80)	0.619
Diabetes mellitus		7 (30.4)	1 (20)	1.000
Hypercholesterolemia		14 (60.9)	5 (100)	0.144
Regular cigarette smoking		7 (30.4)	2 (40)	1.000
Other risk factors	Yes	5 (21.7)	2 (40)	0.574
	No	18 (78.3)	3 (60)	
Treatment	IV heparin + warfarin	18 (78.3)	4 (80)	0.889
	IV heparin + ASA	0	0	
	ASA	4 (17.4)	1 (20)	
	LMWH + warfarin	0	0	
	LMWH + ASA	0	0	
	IV thrombolysis	1 (4.3)	0	
Duration of hospital stay (mean±SD day) (min-max)		12.83±6.98 (1-25)	14.0±8.972 (6-28)	0.857

Data are presented as n (%), except age, gender, and hospital stay. SD: standard deviation; CAD: carotid artery dissection; TIA: transient ischemic attack; mRS: modified Rankin scale; IV: intravenous; ASA: acetylsalicylic acid; LMWH: low molecular-weight heparin

In this study, the mean age of deceased patients was higher than that of surviving patients with CCAD and patients with VAD, whereas the mean age did not differ between the deceased and surviving patients with CAD. In young and middle-aged patients, CCAD is the cause of up to one in four strokes, with peak prevalence in the fifth decade of life (1). However, data from the literature reveal that CCAD affects all age groups, including infants, with reported patients ranging in age from 8 months to 95 years (5,11).

In the present study, severe disability at admission (mRS score 3-5) was more common in deceased patients than that in surviving patients with CAD and VAD, and severe disability at admission was a mortality predictor in both groups. In a large series of 195 patients with VAD, a low National Institutes of Health Stroke Scale score at admission and younger age were predictors of favorable clinical outcomes (8). A prospective study found that among patients with VAD, those with ischemic events had a higher mean age than those without ischemic events (16).

Although the initial severity of stroke has been reported to be related to a poor outcome in patients with both CAD and VAD (6,8,7,9,10), it has not been previously identified as a mortality predictor in patients with CAD or VAD. It is essential to quantify stroke severity in order to interpret outcome in stroke studies. The National Institutes of Health Stroke Scale has been used as an objective measurement of stroke severity (17). However, we used the mRS as a measurement of disability from stroke because patients in the present study were included over a long time period and had been examined by different physicians using a variety of methods. mRS has been demonstrated to have acceptable inter-rater reliability (15,18).

The major presentations of both CCAD and VAD were ischemic stroke in deceased patients and local symptoms in surviving patients. The presentation did not differ between deceased and surviving patients with CAD. In our study, stroke was a predictive factor for mortality in patients with VAD. Furthermore, in this study, no patient presented with SAH.

Table 4. Comparison of demographical and clinical characteristics between surviving and deceased patients with vertebral artery dissection

Variable		Surviving-VAD (n=32) n (%)	Deceased-VAD (n=7) n (%)	p value
Age (mean±SD, year) (min-max)		55.19±13.44 (34-82)	70.29±12.23 (46-80)	0.01
Gender (female/male)		10/22	1/6	0.649
Pre-stroke disability	mRS score 0-2	32 (100)	7 (100)	
	mRS score 3-5	0 (0)	0 (0)	
Disability at admission	mRS score 0-2	29 (90.6)	3 (42.9)	0.012
	mRS score 3-5	3 (9.4)	4 (57.1)	
Clinical presentation	Stroke	15 (46.9)	7 (100)	0.012
	TIA	4 (12.5)	0 (0)	1.000
	Local signs only	13 (40.6)	0 (0)	0.073
Subgroup of dissection	Vertebral artery-extracranial	30 (93.8)	2 (28.6)	0.001
	Vertebral artery-intracranial	2 (6.3)	5 (71.4)	0.001
Nature of dissection	Spontaneously	25 (78.1)	5 (71.4)	0.653
	Minor trauma	7 (21.9)	2 (28.6)	
Hypertension		14 (45.2)	6 (85.7)	0.093
Diabetes mellitus		8 (25)	2 (28.6)	1.000
Hypercholesterolemia		15 (46.9)	6 (85.9)	0.098
Regular cigarette smoking		10 (31.3)	1 (14.3)	0.649
Other risk factors	Yes	11 (34.4)	2 (28.6)	1.000
	No	21 (65.6)	7 (71.4)	
Treatment	IV heparin + warfarin	16 (50)	4 (57.1)	0.914
	IV heparin + ASA	0	0	
	ASA	10 (31.3)	2 (28.6)	
	LMWH + warfarin	4 (12.5)	1 (14.3)	
	LMWH + ASA	2 (6.2)	0	
	IV thrombolysis	0	0	
Duration of hospital stay (mean±SD, day) (min-max)		15.66±11.02 (3-64)	23.57±15.44 (9-54)	0.857

Data are presented as n (%), except age, gender, and hospital stay. SD: standard deviation; VAD: vertebral artery dissection; TIA: transient ischemic attack; mRS: modified Rankin scale; IV: intravenous; ASA: acetylsalicylic acid; LMWH: low molecular-weight heparin

Dziewas et al. (4) also found that the major clinical presentation of CCAD was ischemic stroke that affected 86% of patients with no significant difference between patients with CAD and VAD. They reported that stroke and arterial occlusion were independent factors associated with poor outcomes. However, because only one (1%) patient died in that study, no association between ischemic stroke and mortality in patients with CCAD could be evaluated (4).

In the present study, intracranial VAD occurred with a higher frequency in deceased patients and was a significant predictor for in-hospital mortality in patients with CCAD by both univariate and multivariate logistic regression analyses. However, there was no apparent association between mortality and intracranial or extracranial CAD.

In a study that included 16 patients with VAD, intracranial dissection had a poorer prognosis than extracranial dissection. In addition, significant factors for a poor outcome (i.e., disability with mRS scores >3) were the initial severity of stroke and a bilateral location of the dissection (12). In contrast, a study in 35 patients with VAD found no significant correlation between dissection location and functional outcome (6). Moreover, neither intracranial VAD nor bilateral VAD predicted an unfavorable clinical outcome in a large series of 195 patients with VAD (8).

Intracranial VAD may present with focal neurological deficits due to vertebrobasilar artery ischemia and SAH. One study concluded that intracranial VAD was typically associated with severe neurological deficits and patients with SAH had poor prognosis (5). Other studies have suggested that the natural course and outcome of the patient strongly depends on the initial clinical presentation. Many patients presenting with ischemic symptoms have a favorable outcome. While an unruptured intracranial VAD may have a relatively benign course with a high probability of spontaneous angiographic cure, a high mortality rate has been reported among patients with a ruptured VAD (13).

Table 5. Predictors of deceased patients with vertebral artery dissection

Variable	Odds ratio (95% CI)	p value
Age		
(0) ≤45 y	1.52 (1.18-1.95)	0.01
(1) >45 y		
Disability at admission		
(0) mRS score 0-2	6.09 (1.74-21.35)	0.012
(1) mRS score 3-5		
Clinical presentation		
(0) Local signs	2.13 (1.47-3.08)	0.012
(1) Stroke		
(0) Vertebral artery-extracranial	11.42 (2.75-47.34)	0.001
(1)Vertebral artery-intracranial		

(1), risk factor; (0), not a risk factor. mRS, modified Rankin scale; 95% CI, 95% confidence interval

In the present study, the frequencies of HT and HC were independently related to mortality in patients with CCAD. However, we found no significant difference in the frequency of HT or HC between CAD and VAD. This may be because of the small numbers of patients in the subgroups.

In a study, it was shown that HT and HC were risk factors for spontaneous CAD (10). Dziewas et al. (4) reported frequencies of 25% and 40% for HT and HC, respectively, in patients with CCAD. HT frequency in our patients with CCAD was double and that of HC 1.5-fold higher than those reported by Dziewas et al. (4).

This study has several limitations. First, the study enrolled a relatively small number of patients with CCAD. Second, the patients included in this study were retrospectively evaluated.

Despite these limitations, our study also has several strengths. To our knowledge, this is the first report directly focusing on mortality and its predictive factors in patients with CCAD and its subgroups. The mortality rate in patients with CAD was 1.5 times higher than that previously reported. Severe disability at admission was a mortality predictor in both CAD and VAD. Although the initial severity of stroke has been reported to be related to poor outcomes in patients with CAD and VAD, it has not previously been directly identified as a mortality predictor in patients with CAD or VAD.

In conclusion, larger systematically designed prospective clinical studies are required to clarify the true incidence of mortality and its predictors in both the short- and long-term.

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