Journal of Stroke and Cerebrovascular Diseases 34 (2025) 108417

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstroke

Stroke and cervical artery dissection and/or aneurysm: 2019-2021 Chilean hospital-based national registry

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ARTICLE INFO

Keywords:
Cervical artery dissection
Stroke
Cervical artery aneurism
Risk factors
Carotid artery dissection
Vertebral artery dissection

ABSTRACT

Background: Cervical artery dissection is one of the main causes of stroke in young adults, yet the characteristics of patients have been mainly described in Caucasian populations. We aimed to identify patients' characteristics associated with stroke among cervical artery dissection patients in Chile.
Methods: We conducted a retrospective analysis of a national hospital-based database in Chile between 2019 and 2021. Patients with cervical artery dissection or aneurysm (CeDA) were identified using ICD-10 codes I72.0 (carotid artery) and I72.6 (vertebral artery); stroke events were classified using codes I60–I64. We performed multivariable logistic regression to evaluate the association between patients' characteristics and stroke occurrence. We further performed Poisson regression to assess the impact of the coronavirus pandemic on CeDA admissions.
Results: Of 2,647,398 hospital discharges, we identified 597 CeDA patients (mean [SD] age 57 [15] years; female 384, 64 %). Stroke occurred in 233 (37 %) patients, with ischaemic stroke accounting for 71 % of these events. In the multivariable analysis, stroke occurrence was associated with vertebral artery involvement (OR 2.89; 95 %CI 1.76-4.77), atrial fibrillation (2.25; 1.03-4.90), hypertension (1.85; 1.25-2.74), male sex (1.80; 1.24-2.62) and current smoking (1.78; 1.13-2.80). Hospital admissions for CeDA declined in 2020 (rate ratio [RR] 0.69; 95 %CI 0.57–0.85) and 2021 (0.76; 0.63–0.92), compared with 2019.
Conclusions: In this Chilean hospital-based database, stroke occurrence among CeDA patients was linked to male sex, vertebral artery involvement, hypertension, current smoking, and atrial fibrillation. Further research is needed to understand the underlying mechanisms and its association with patient prognosis.

Introduction

Although cervical artery dissection or dissecting aneurysm (CeDA) is an infrequent condition with an annual incidence between 2.9-4.6 per 100,000 person-years,[1,2] it represents 15 % to 25 % of ischemic stroke in young adults.[3] Risk factors for CeDA had been previously described encompassing genetic components, cervical trauma, migraine, connective tissue disorders, and vascular risk factors such as hypertension and smoking habits.[4,5] Nonetheless, clinical variables associated to cerebrovascular outcomes in CeDA patients remain poorly understood. Furthermore, most of the studies have been focused on European or North American populations, leaving underrepresented populations with a deficit on epidemiological data.

Aims

We aimed to describe patients' characteristics associated with the presentation of stroke in patients with CeDA in a hospital-based national

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https://doi.org/10.1016/j.jstrokecerebrovasdis.2025.108417
Received 12 June 2025; Received in revised form 2 August 2025; Accepted 5 August 2025
Available online 6 August 2025

registry.

Methods

This is a retrospective cohort study based on the Chilean International-Refined Diagnosis Related Groups (IR-DRG) database. The IR-DRG is an international, standardized payment method system that recollects data from hospital discharges and further categorizes patients into homogenous groups according to their complexity and associated costs.[6] In Chile, the IR-DRG system includes 65 medium to high complexity hospitals, capturing the largest and most advanced institutions in the country, equipped with the diagnostic tools and clinical expertise necessary to identify and manage cervical artery dissection. In the year 2019, these hospitals contributed to 70 % of the operational expenditure in the public health scheme.[7] The reimbursement system incentivizes comprehensive and accurate clinical coding. Furthermore, coding is performed by trained nurses with specialized expertise, who extract clinical information directly from patient records. This study was conducted and reported according to the STROBE statement for observational studies (Table S1).[8]

We included all patients (age ≥18 years) registered in the Chilean IR-DRG with CeDA as diagnosis, between January 1, 2019, and December 31, 2021. There were no patients with missing information in sex, age, date of admission or discharge to be excluded. In cases with multiple admissions, we solely included the first event, except for admissions occurred within 24 hours of the discharge of the index event, which were considered as a continuous hospitalization. Regarding the genetic composition of Chilean population, it reflects a Caucasian-Native American admixture initiated during the Spanish conquest in the mid-16th century, with a minor African contribution introduced in the 17th century and subsequent European migrations in the 19th and 20th centuries, with a 45 % global ancestry proportion for the Chileans consisting in Native-American component.[9]

CeDA was defined as CeDA of the carotid artery (CA) and/or CeDA of the vertebral artery (VA) in any of the diagnosis records, with their corresponding International Classification Diseases, Tenth version code 2015 (I72.0; I72.6 respectively).[10] Because of the codification system engaged on the IR-DRG, and in lack of alternatives, the ICD-10 code used did not allow to distinguish between cervical artery dissection and/or aneurism. Demographic information, medical history, treatment, and in-hospital complications were retrieved from the database. The primary outcome was the presence of stroke defined with its corresponding ICD-10 codes: I60, I61, I62, I63, I64. Low socioeconomic status (SES) was obtained through the national health insurance assigned group, which categorizes individuals based on their income into four main types; low SES was assigned to those without income or those with income below the minimum national wage.

Given the impact of the coronavirus pandemic on the years 2020 and 2021, we identified all the COVID-19 hospitalizations in the respective years, with the corresponding ICD-10 code: U07.1 and U07.2, to evaluate if CeDA admissions fluctuated during this period.

Statistical analysis

Comparisons of baseline patients' characteristics were performed using chi-squared or T-test when required. To evaluate the independent association of risk factors and the presence of stroke, we performed a multivariable logistic regression. Further sensitivity analysis was performed excluding those patients with trauma, subarachnoid hemorrhage or have a record of aneurysm repair (n = 166). The impact of the coronavirus pandemic on CeDA hospitalizations was evaluated performing a Poisson regression analysis for each of the quarterly period from 2020 to 2021, using the corresponding period in 2019 as a baseline reference. CeDA hospitalization rate was calculated using the yearly national population according to the National Statistics Department. [11] Results are reported as odds ratio (OR) or rate ratio (RR), with 95 % confidence intervals (CI). Significance level was set at $P < 0.05$. All data were analyzed using STATA version 18.0.

Results

Of the 2,647,398 IR-DRG hospitalizations registered from 2019 to 2021, 674 CeDA hospitalizations were identified. After excluding those under 18 years old ($n = 11$) and duplicated events ($n = 76$), 597 patients were retained for analysis. (Fig. 1) The mean age was 57.84 ± 15.18, females accounted for 64.32 % (384/597) and the most common localization was carotid artery (85.43 %; 510/597). Only 2 patients (0.34 %) were registered as having both carotid and vertebral CeDA localization. Overall, 37.35 % (233) presented a stroke with ischemic stroke being the most common subtype (70.85 %;158/233), followed by subarachnoid hemorrhage (28.7 %; 64/233). Prevalent comorbidities were hypertension (54.27 %), diabetes mellitus (18.59 %) and current smoking habits (18.43 %). During hospitalization, median hospitalization length was 7 days (IQR 3-16), most patients underwent a brain computed tomography (CT) (83.03 %) and 4.69 % died at hospitalization. Table 1 shows baseline information for the overall group and by stroke presentation.

Relative to CeDA patients without stroke (CeDA-nonS), age-adjusted analysis CeDA showed that patients with stroke (CeDA-S) were most frequently males (OR 2.22; 95 %CI 1.56-3.15), had no difference in age of presentation (P = 0.122) and, although CA involvement was more prevalent (76.23 %), CeDA-S patients had higher likelihood of VA compromise (OR 3.27; 95 %CI 2.04-5.24). Regarding prior medical history, CeDA-S patients had more hypertension (OR 1.88; 95 %CI 1.30-2.72), current smoking habits (OR 1.87; 95 %CI 1.22-2.86) and atrial fibrillation (2.32; 95 %CI 1.10-4.88) when compared to CeDA-nonS. CeDA-nonS patients exhibited a two-fold increase in the prevalence of migraine and connective tissue diseases, however, it was not statistically significant. We found a similar mortality rate between CeDA-S and CeDA-NS. Patients with CeDA-nonS who died during hospitalization had diagnoses of sepsis and other infectious conditions (7/17), trauma (4/17) and aortic dissection or other vascular conditions (6/17).

In the multivariable analysis, males (OR 1.80; 95 %CI 1.24-2.62), HT (OR 1.85; 95 %CI 1.25-2.74), AF (OR 2.25; 95 %CI 1.03-4.90), current smoking habits (OR 1.78; 95 %CI 1.13-2.80) and VA localization (OR 2.89; 95 %CI 1.76-4.77) were associated with CeDA-S compared to CeDA-nonS (Fig. 2). Results from the sensitivity analysis excluding those with trauma or subarachnoid hemorrhage did not differ (Tables S3 and S4).

Since the study period was heavily impacted from the global COVID-19 pandemic because of SARS-CoV-2 virus, further evaluation of its influence on CeDA hospitalizations was carried out. Compared to the admission rate during 2019, CeDA admissions were 31 % lower during 2020 and 24 % lower in 2021 (RR=0.69; 95 % CI 0.57-0.85 and RR=0.76; 95 % CI 0.63-0.92 respectively) (Table 2). Quarterly period evaluation showed that the reduction on CeDA hospitalizations was more pronounced on the fourth quarter of 2020 to the second quarter of 2021, which coincided with the second COVID-19 wave in Chile (Fig. 3). Given the impact of the pandemic, a yearly examination of the patient's characteristics associated to CeDA-S was conducted. In the pre-COVID year (2019), predictors of stroke included hypertension and vertebral localization of CeDA. While male sex and current smoking emerged as significant predictors during the pandemic period (2020–2021).No additional associations, beyond those already identified, emerged from the individual yearly analyses (Tables S5 and S6).

Discussion

In this Chilean cohort of hospitalized patients with CeDA during the years 2019 through 2021, the predominance of carotid involvement and female sex were evident. Five characteristics were associated to stroke presentation: male sex, VA localization, hypertension, current smoking

Table 1
Baseline characteristics of CeDA patients by presence of stroke.

	Overall	CeDA without stroke	CeDA with stroke	*P value*
	597	374; 62.65 %	233; 37.35 %	
Sociodemographic characteristics				
Age, mean ± SD	57.84 ± 15.18	57.10 ± 15.45	59.08 ± 14.67	0.122
Females, n (%)	384 (64.32)	265 (70.86)	119 (53.36)	<0.001
Low socioeconomic status, n (%)	103 (17.25)	42 (18.83)	61 (16.31)	0.430
Risk Factors, n (%)				
Hypertension	324 (54.27)	181 (48.40)	143 (64.13)	<0.001
Diabetes Mellitus	111 (18.59)	61 (16.31)	50 (22.42)	0.063
Dyslipidemia	79 (13.23)	51 (13.64)	28 (12.56)	0.706
Current Smoking	110 (18.43)	57 (15.24)	53 (23.77)	0.009
Obesity	60 (10.05)	34 (9.09)	26 (11.66)	0.313
Chronic kidney disease	35 (5.86)	24 (6.42)	11 (4.93)	0.455
Migraine	13 (2.18)	9 (2.41)	4 (1.79)	0.62
Ischemic heart diseases	18 (3.02)	7 (1.87)	11 (4.93)	0.034
Atrial fibrillation	31 (5.19)	13 (3.48)	18 (8.07)	0.014
Conective tissue diseases	15 (2.51)	12 (3.21)	3 (1.35)	0.159
Presentation, n (%)				
Carotid CeDA	510 (85.43)	340 (90.91)	170 (76.23)	<0.001
Vertebral CeDA	89 (14.91)	35 (9.36)	54 (24.22)	<0.001
Stroke by subtype*				
Ischemic stroke	158 (26.47)	NA	158 (70.85)	NA
Intracerebral Hemorrhage	28 (4.69)	NA	28 (12.56)	NA
Subarachnoid Hemorrhage	64 (10.47)	NA	64 (28.70)	NA
Undetermined	3 (0.50)	NA	3 (1.35)	NA
Transient ischemic attack	20 (3.35)	15 (4.01)	5 (2.24)	0.245
Trauma	59 (9.88)	43 (11.50)	16 (7.17)	0.087
Diagnostic test, n (%)				
Brain or Neck MRI	119 (19.93)	66 (17.65)	53 (23.77)	0.07
Brain or Neck CT	496 (83.08)	283 (75.67)	213 (95.52)	<0.001
Brain or Neck ecography	29 (4.86)	11 (2.94)	18 (8.07)	0.005
Hospitalization				
Hospitalization days, Median (IQR)	7 (3-16)	5.5 (2-12)	11 (6-21)	<0.001
In-hospital Mortality, n (%)	28 (4.69)	17 (4.55)	11 (4.93)	0.829

Abbreviations: CeDA=cervical artery disection and/or aneurysm; IQR=interquartile range; SD= standart desviation; MRI= magnetic resonance imaging; CT= computed tomography.(*) Numbers may not add up due to patients with two subtypes.Bold denotes stadistically significant results.

and atrial fibrillation.

The mean age in this cohort was 57.8 years, which is older than those previously reported from population-based studies in the United States and France, with an average of 50 years.[1,12] While this may reflect inherent population differences, prior research conducted in Mexico reported an even younger average presentation age of 35.4 years.[13] Additionally, a previous national study with prospective single-center data collection showed a mean age of 41 years.[14] We hypothesized that the older age in our cohort could be attributed to the nature of our database, since only hospitalized patients were included. Younger

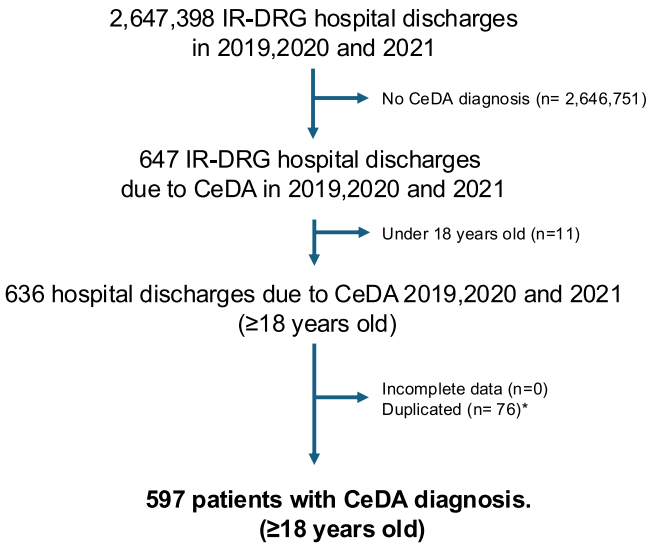

Fig. 1. Study set-up flowchart.
Abbreviation: CeDA= Cervical dissection and/or aneurysm; IR-DRG= Diagnosis related group database. *Duplicated due to multiple hospital discharges only the first event was included.

patients may present with milder symptoms and be treated outside the hospital ward or may not be diagnosed due to the high suspicion index required. Indeed, a statewide cohort study in Florida and New York found that younger age was independently associated with higher chances of emergency department misdiagnosis of CeDA.[15]

The high proportion of females in our findings is in line with recent studies that have shown female predominance of 50-56 %.[1,12] Nonetheless, the absolute differences are smaller than our results. Regional studies present conflicting results: the aforementioned national study reported 60.1 % females patients,[14] which contrast with the Mexican cohort with only 46.2 %.[13] We were unable to gather information on sex-specific risk factors such pregnancy, postpartum and oral contraception which had been linked to CeDA.[16] However, given the median age in our study, we believe it's unlikely that females in our cohort were primarily on this group. Our current finding could be explained by other female-specific risk factors such as fibromuscular dysplasia, differences in triggering factors, and genetic components. Further research is warranted to determine any underlying factors that could determine female predisposition to CeDA.

While we had a predominance of female sex, male sex was independently associated to stroke presentation, which is in line with previous reports.[4,14,17] The role of estrogens has been proposed as an explanation,[17] with females having better endothelial function and antithrombotic capacity, however given the older age in our cohort the likelihood of estrogen protection in the postmenopausal stage has yet to be determined and our results must be interpreted with caution.

Classical stroke risk factors were also associated to stroke in this CeDA cohort. Current smoking has been previously described,[17,18] with impaired endothelial function being an enhancer of a pro-thrombogenic environment that can increase the risk of cerebral embolization in these patients.[17] The role of hypertension in CeDA has been mainly described on the risk of ischemic events, thus our results could be the reflection of the incorporation of other subtypes in the analysis. However, the higher prevalence in hypertension and the older age at presentation in our cohort raises the question whether the endothelial changes induced by hypertension alongside the age-mediated arterial stiffness,[19] which CeDA patients have been proposed to have a constitutional elevated carotid stiffness,[5,20] could intensify the narrowing of the arterial luminal wall and endothelial abnormalities in dissected vessels, promoting clot formation and subsequent embolization. The relationship between atrial fibrillation and stroke in CeDA patients has not been clearly reported so

	Stroke			
	CeDA-nonS	CeDA-S	Adjusted OR(95%CI)*	*P* value
Age			1.006 (0.99-1.02)	0.305
Males	109/374	104/223	1.80 (1.24-2.62)	0.002
Low socioeconomic status	42/374	61/223	1.09 (0.68-1.75)	0.714
Hypertension	181/374	143/223	1.85 (1.25-2.74)	0.002
Atrial Fibrillation	13/374	18/223	2.25 (1.03-4.90)	0.041
Current smoking	57/374	53/223	1.78 (1.13-2.80)	0.021
Vertebral CeDA	35/374	54/223	2.89 (1.76-4.77)	<0.001

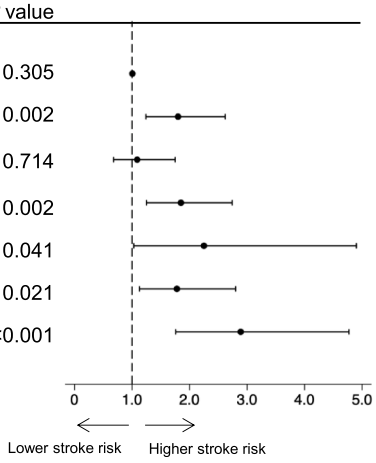

Fig. 2. Independent predictors of stroke in cervical artery and/or aneurysm patients.
(*)Adjusted by all variables presented in the graphic. Results are presented in Odds ratio with 95 % confidence Interval. Abbreviations: OR=odds ratio. CI=Confidence Interval. CeDA=cervical artery dissection and/or aneurysm.

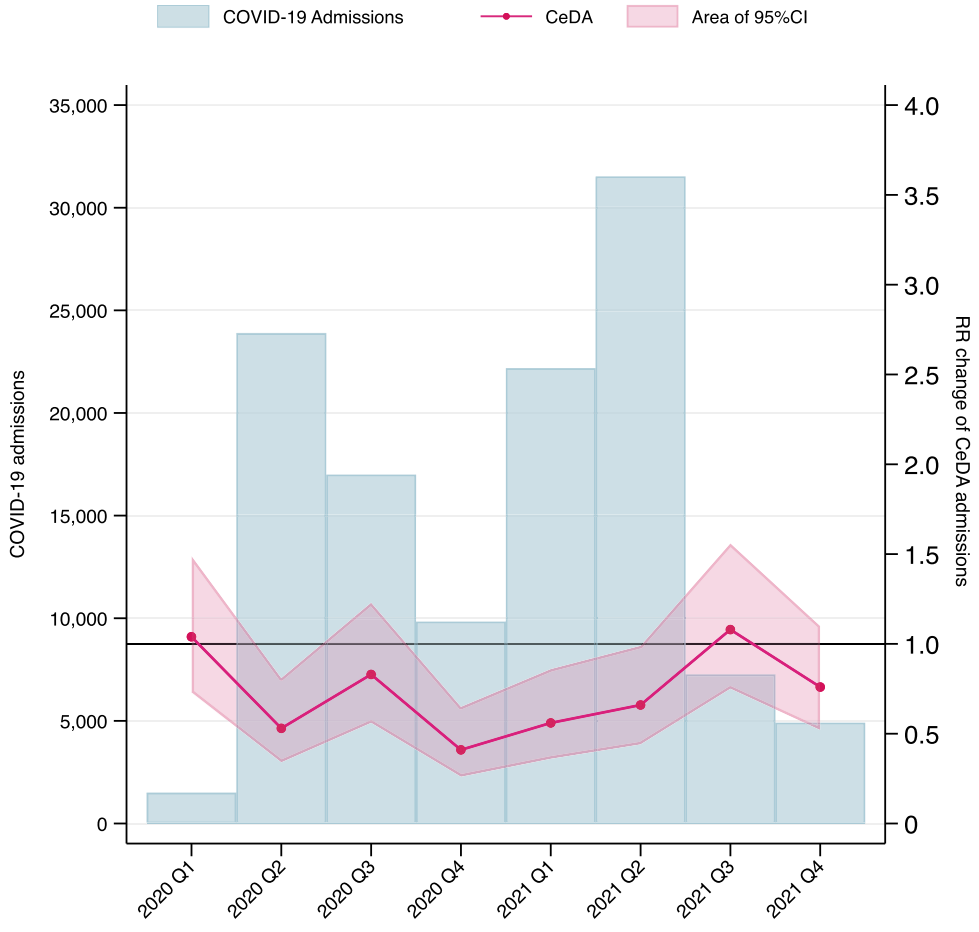

Fig. 3. Quarterly change rate ratio of CeDA patients admission taking 2019 as reference.
Rate ratio calculated taking the same quarter period of 2019 as reference. Abbreviations: RR=Rate ratio. CI=confidence Interval.

far. Its association with endothelial damage may also explain this relationship with stroke in patients with CeDA; however, it is possible that CeDA patients have cardioembolic strokes related to AF, without necessarily being causally or pathophysiologically linked to CeDA.

Carotid presentation was the most common localization in our cohort and this predominance has been reported before.[1,3] A post-hoc analysis of the CADISP clinical trial found that the frequency of internal carotid artery CeDA increases with age, with a 3.6-fold greater risk in those patients aged 55 or above,[21] that is in line with our older cohort and stronger carotid CeDA compromise. Conversely, accurate diagnosis of

VA compromise requires a higher index of suspicion and adequate imaging interpretation, thus our results might not reflect its actual prevalence. However, VA localization revealed to be associated to stroke in CeDA in agreement with previous reports.[22,23] A study evaluating 186 consecutive patients with spontaneous VA dissections showed an increased risk of ischemia with increasing age,[17] thus the age of our cohort could further explain our results. Regarding CeDA outcomes, we found similar in-hospital mortality rate between CeDA-S and CeDA-nonS in this cohort. This was related to CeDA severe cases presenting with other conditions such as sepsis and infections, trauma and other CV disorders not coded as stroke. This low acute mortality rate is in line with previous reports.[24]

We observed a reduction of up to 31 % in hospitalizations among patients with CeDA during the COVID-19 pandemic. While the predictors of stroke identified in yearly analyses were largely consistent with those in the pooled dataset, male sex and current smoking were not associated with stroke in the pre-pandemic year (2019). As previously mentioned, both male sex and current smoking are well-established risk factors for stroke.[4,14,17,18] Their absence of association in the pre-pandemic data may be attributable to limited statistical power due to year-by-year stratification. However, it is also plausible that during the pandemic, healthier individuals avoid seeking medical care, potentially altering the risk profile of those who were hospitalized.(Table 2).

To the best our knowledge, this is the largest cohort study on CeDA patients in Latin America including patients who were generally underrepresented in other reports, and the large sample size of this registry allowed us to produce significant epidemiological data on an understudied disease and underrepresented populations. We acknowledge this study has several limitations. First, the absence of a separate code for cervical artery dissection and cervical artery aneurysm made impossible the distinction between these two entities. This is because the IR-GRD was codified using the ICD-10 code updated in 2015. However, the code includes only aneurysms in cervical arteries and not cerebral compromise, so it is plausible that most of the cervical aneurysms included in the database are related to dissection (pseudoaneurysms). We tried to overcome this, by performing a subsequent sensitivity analysis, which didn't show different results. Also associated with the secondary database use and lack of specific registry, analyses about multivessel involvement were not possible, and we had no access to clinical outcomes other that death. Second, we acknowledge that causality cannot be inferred from this hospital registry. Nonetheless, we considered it valuable to proceed with the analyses, as given the relatively young age of the cohort and the clinical context in which both conditions are diagnosed during the same hospital admission, it is more plausible that the cervical artery dissection is related to the stroke, rather than the stroke being due to another etiology with a concurrent incidental diagnosis of CeAD. Third, research using electronic health record databases also depends on the accuracy of clinical coding. The DRG system relies on trained coders with specific expertise in ICD-10 coding, who extract clinical information directly from patient records to promote completeness and consistency. The accuracy of clinical diagnoses recorded in DRG systems has been evaluated in other settings, including a study in China,[25] where error rates in coder-assigned data were found to be substantially lower than those in physician-assigned data, an issue more commonly observed in other types of electronic health record systems. Nonetheless, the potential for misclassification, particularly due to limited access to imaging data and variability in diagnostic practices across centers, must be acknowledged. In Chile, nationally linked imaging databases are currently unavailable due to the fragmentation of the healthcare system. Therefore, our approach provides the most comprehensive nationwide perspective currently feasible. Lasty, the use of a hospital-based database under-represents patients treated outside the hospital ward, there might be other not registered factors that we are not taken into consideration and the clinical details of presentation and outcome were not available.

In summary, in this large national hospital cohort of predominantly carotid female CeDA, our findings suggest that male sex, VA localization and vascular risk factor like hypertension, current smoking and atrial fibrillation were associated to stroke presentation in CeDA patients. Further research is needed to understand the underlying mechanisms behind it as well as its association with patients' prognosis.

Table 2
CeDA hospitalization rate by year and rate ratio compared to 2019.

Year	Events	Population at risk*	Hospitalization rate per 100,000 population	RR (95 % CI)
2019	235	14,646,285	1.60	*reference*
Q1	58	14,646,285	0.39	*reference*
Q2	59	14,646,285	0.40	*reference*
Q3	55	14,646,285	0.37	*reference*
Q4	63	14,646,285	0.43	*reference*
2020	168	14,982,343	1.12	0.69 (0.57-0.85)
Q1	62	14,982,343	0.41	1.04 (0.73-1.49)
Q2	32	14,982,343	0.21	0.53 (0.34-0.81)
Q3	47	14,982,343	0.31	0.83 (0.56-1.23)
Q4	27	14,982,343	0.18	0.41 (0.26-0.65)
2021	187	15,200,840	1.23	0.76(0.63-0.92)
Q1	34	15,200,840	0.22	0.56 (0.36-0.86)
Q2	41	15,200,840	0.26	0.66 (0.44-0.99)
Q3	62	15,200,840	0.40	1.08 (0.75-1.56)
Q4	50	15,200,840	0.32	0.76 (0.52-1.10)

RR=rate ratio. CI=Confidence interval. (*) Yearly national population according to the National Statsitics Deparment. Note= IRR calculations were based on patients with admission on the respective evaluated years, since the database is based on discharges, seven patients who were admitted on 2018 but discharge on 2019 were excluded from this analysis.

CRediT authorship contribution statement

Ma Ignacia Allende: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Paula Munoz Venturelli:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Enrico Mazzon:** Writing – review & editing, Conceptualization. **Alejandro Brunser:** Writing – review & editing, Conceptualization. **Iris Delgado:** Writing – review & editing. **Boris Rebolledo:** Writing – review & editing, Conceptualization.

Declaration of competing interest

PMV receives research grants from ANID Fondecyt Regular 1221837, Pfizer and Boehringer Ingelheim. The other authors declare no conflict of interest.

Acknowledgments

None.

Data availability

All data used in these analyses are publicly available from the domain: https://public.tableau.com/views/PropuestaTableroGRD/PropuestaTableroGRD?%3AshowVizHome=no#1. Additionally, all data collected for the study and posterior results are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2025.108417.

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