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ORIGINAL PAPER

Factors Associated with Severe Carotid Artery Stenosis in a Population with One of the Highest Incidences of Ischemic Stroke in Europe – Single National Center Analysis

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ABSTRACT

Introduction: *Despite significant advances in its prevention and acute-phase treatment, stroke is still one of the leading causes of disability and death worldwide. Ischemic stroke accounts for 80 to 87% of all strokes, with 15-30% of cases being caused by extracranial carotid artery (CA) stenosis.*

Methods: *This is an observational, cross-sectional, single-center, prospective, registry-based study. The current research presents the preliminary results after analyzing the demographic features, biological data, and cardio- and cerebro-vascular risk factors of the first 74 patients included in the first "Romanian registry for cervical and cerebral arterial stenosis."*

Results: *In our group of patients, the severity of carotid artery stenosis was related to fibrinogen, total cholesterol, and triglyceride blood levels. Moreover, patients who underwent carotid artery stenosis were more prone to having peri-procedural complications if they had a low blood platelet count. Concerning the associated pathologies of patients with severe carotid atheromatosis, the risk of having lower cognitive abilities was higher in subjects with atrial fibrillation, regardless of the severity of carotid artery stenosis.*

Conclusion: *The presented study brings essential information about a population more prone to cerebral ischemic events than that of most other countries. All data obtained until this moment and which will further result from analyzing the clinical, demographic, and biological features of patients included in this registry should be used for implementing populational strategies for preventing further strokes.*

Keywords: carotid artery stenosis, national registry, stroke, carotid artery stenting.

List of abbreviations:

TOAST=Trial of Org 10172 in acute stroke treatment; CA=carotid artery; CAS=carotid artery stenting; CAE=carotid artery endarterectomy; mg=milligrams; dL=deciliters; CKD-EPI=estimated filtrate rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration); DALY=disability-adjusted life-years; CTA=computed

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tomography angiography; AGT=altered glucose tolerance; CKD=chronic kidney disease; AF=atrial fibrillation; TIA=transient ischemic attack; MMSE=mini-mental state exam; CDT=clock drawing test; EGFR=estimated glomerular filtration rate; HbA_{1C}=glycosylated hemoglobin; ESR=erythrocyte sedimentation rate; VaD=vascular dementia.

INTRODUCTION

Stroke is still one of the leading causes of disability and death worldwide, despite significant advances in its prevention and acute-phase treatment (1). Ischemic stroke account for 80 to 87% of all strokes (1, 2), with 15-30% of ischemic strokes being caused by extracranial carotid artery (CA) stenosis (3-5).

Romania has been and continues to be in top five countries concerning the incidence and prevalence of stroke, mortality related to ischemic stroke, and disability-adjusted life-years (DALYs) due to stroke. Several epidemiological studies showed a decrease in the incidence of stroke and number of stroke-related deaths (11.3% and 27%, respectively) in Romania from 1990 to 2016 (6). Nevertheless, according to the King's College London study published in 2017, Romania was still ranking 3rd in Europe when considering the incidence of stroke and 2nd for the number of deaths due to stroke (7). Therefore, there is an urgent need for a rigorous characterization of risk factors that play a role in maintaining a high incidence of stroke in this group of patients. A thorough characterization of the Romanian population could contribute to the development and implementation of a large-scale populational screening and interventional epidemiologic program. Moreover, long-term monitoring of patients with CA stenosis and those treated either by percutaneous angioplasty and stenting, endarterectomy, or medical therapy, could improve the quality of health providers' medical services and could help establish the cost-effectiveness of each treatment.

This paper presents the preliminary results after analyzing the demographic features, biological data, and cardio- and cerebro-vascular risk factors of the first 74 patients included in the first "Romanian registry for cervical and cerebral arterial stenosis."

MATERIALS AND METHODS

The "Romanian registry for cervical and cerebral arterial stenosis" was developed within the Competitivity Operational Program 2014-2020 co-funded by the European Fund for Regional Development. Five national centers from Romania included patients with hemodynamically significant symptomatic or asymptomatic carotid artery stenosis. For the current study, only data resulting from patients examined in the University and Emergency Hospital of Bucharest was used.

Study design

This is an observational, cross-sectional, single-center, prospective, registry-based study. For the current research, only data from patients included in the University and Emergency Hospital of Bucharest were used. The study protocol was approved by the local ethics committee and was in accordance with the Declaration of Helsinki. Final data analyses are expected at the end of the year 2020.

The primary goal of this study was to assess the prevalence and role of the most critical risk factors in Romanian patients with hemodynamically significant carotid artery stenosis and to determine which factors contribute to the severity of symptomatic carotid artery stenosis. Secondary endpoints included determining the risk factors that predispose to complications in patients who undergo carotid artery stenting (CAS) or carotid artery endarterectomy (CAE).

Registry group and data collection

In this current ongoing study, we included all consecutive patients who were evaluated using cervical-cerebral digital subtraction angiography (CCDSA) and had hemodynamically significant stenosis in at least one of the carotid arteries, between September 2018 and January 2020. A hemodynamically significant CA stenosis was considered equal or greater than 50%, evidenced by ultrasound – using the NASCET method of calculating the degree of arterial stenosis (8) – or computed tomography angiography (CTA) examinations. Patients suffering from concomitant

neoplastic diseases, those who were clinically unstable or had a life expectancy shorter than five years were excluded from the study.

All patients signed the written informed consent and were interviewed regarding their lifestyle, prior pathologies, and medications before CCDSA.

Demographical and clinical data was collected using standardized questionnaires and included patients' age, gender, place of living (rural or urban) and smoking status [non-smoker, active smoker, and past-smoker – for the last two categories, the pack-year index was calculated (9)]. History of associated pathologies and other cardiac and cerebral risk factors was also recorded in the registry, such as the presence of hypertension, diabetes, altered glucose tolerance (AGT), chronic kidney disease (CKD), atrial fibrillation (AF), dyslipidemia, body mass index (BMI) (10), history of cerebrovascular events – hemorrhagic/ischemic/transient ischemic attack (TIA) and information regarding their number, arterial territory, TOAST (11), and ASCOD (12) type, previous CAS or carotid artery endarterectomy (CAE), presence of stable or unstable angina, myocardial infarction, and peripheral arterial disease. Data about patients' neurocognitive status has been also collected – previous diagnosis of neurocognitive impairment, the mini-mental-status exam, and the Clock Drawing test (CDT) scores. Blood tests were processed in the same laboratory for all patients. Information regarding the blood tests, which were recorded in the registry for each patient, can be found in Table 1.

Data about imaging studies has been also included in the registry, such as the aspect of the most recent cervical artery ultrasound examination, the latest magnetic resonance imaging, or computed tomography study. After the patients were examined through CCDSA, the degrees of stenosis for both carotid and vertebral artery, as well as the chosen treatment (CAS, CAE or best medical treatment) and possible periprocedural complications (intrastent thrombosis, bradycardia, hypotension, arterial dissection, TIA or stroke, cerebral reperfusion syndrome, myocardial infarction or death) were reported in the registry.

The same three experienced interventional radiologists performed all CCDSAs. Patients having symptomatic carotid artery stenosis, which was equal or greater than 70%, and those with a high risk asymptomatic carotid artery stenosis higher than 70% underwent percutaneous carotid artery angioplasty or CAE, depending on their co-morbidities, clinical and paraclinical profile. For patients with low risk asymptomatic hemodynamically significant carotid artery stenosis, the best medical treatment was chosen. Patients were considered to have symptomatic carotid artery stenosis when an ischemic stroke, TIA, or retinal

TABLE 1. Blood tests included in the registry for each patient

Blood tests	Abbreviation	Units of measure
Hemoglobin	Hb	g/dL
Fasting glycemia	Gly	mg/dL
Creatinine	Cr	
Fibrinogen	Fg	
Uric acid	-	
Total cholesterol	Cho	
Low-density lipoprotein	LDL	
High-density lipoprotein	HDL	
Triglycerides	Tgd	
Glycosylated hemoglobin	HbA1c	Percentiles (%)
Estimated filtrate rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration – CKD-EPI equation)	EGF (CKD-EPI)	mL/min/1.73 m^2
Erythrocyte sedimentation rate	ESR	mm/h
Platelets number	Plt	Gross number
INR	International Normalized Ratio	-

ischemic events ipsilateral with the hemodynamically significant carotid stenosis were present in the last six months preceding the diagnosis of carotid stenosis (13).

Patients who underwent carotid artery stenting were pre-medicated depending on the co-presence or absence of atrial fibrillation (AF). Thus, patients without AF were pre-medicated and also discharged on dual antiplatelet therapy (with Clopidogrel and aspirin) and those ith AF on non-antivitamin-k oral anticoagulant and Clopidogrel. All patients were examined before and after the procedure by the same neurologist. All treatment decisions were made according to the guidelines which were in use at the time of patients' evaluation (14, 15).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 26.0, and Microsoft Excel. For the current study, data resulted from the first 74 patients who were evaluated in the University and Emergency Hospital of Bucharest. After inspecting the pattern of the missing values for each variable, missing variables were inputted with medians or means, depending on the case. Continuous variables were presented as means, along with the standard deviations (SD), whereas categorical variables as percentages or frequencies.

Independent-samples t-test was used to explore the demographic and biological differences between the following sub-groups: (1) patients who had a history of cerebral ischemic events (stroke or TIA) *vs.* asymptomatic patients; and (2) patients who developed complications after cerebral angiography *vs.* patients with no complications. After checking for normal distribution, outliers, linear relationships, and multicollinearity, six biological variables were considered appropriate for analysis in each of the above-mentioned groups: hemoglobin, platelet number, total cholesterol, fibrinogen, triglycerides blood levels, and the estimated glomerular rate. Data are expressed as mean ± standard deviation (SD).

Binomial logistic regression analysis was used to test if clinical or biological variables could predict complications in patients who underwent CAS or CAE.

Multiple regression analysis was used to explore clinical and biochemical variables that could predict the degree of carotid arteries stenosis, but also of the severity of neurocognitive impair ment.

RESULTS

Descriptive statistics

Until February 2020, a total of 74 patients were included in the registry. Of them, 55 (74.3%) were males and 19 females (25.7%). The mean age of the included population was 68.53 years (SD=8.58). Of all patients, 66 (89.1%) had a personal history of ischemic cerebral vascular events (59 subjects had a previous ischemic stroke, four had TIA, and three patients had a history of both TIA and stroke). Thirty-two patients had a history of an ischemic cerebral vascular event in the territory of the left internal carotid artery (ICA); of them, 87.5% had HSLCAS and 50% HSRCAS. Twenty-three patients had a history of stroke or TIA in the right ICA vascular territory; of them, 87% had symptomatic HSRCAS, and 65.2% asymptomatic HLRCAS. The remaining patients had ischemic strokes in the anterior or posterior cerebral artery territory.

Concerning the treatment, 64.86% of patients underwent percutaneous angioplasty and stenting, 31% were discharged on maximal medical treatment (as described in the Method section), and 4.05% were sent for ICA endarterectomy.

Differences between patients with/and without a history of stroke

Independent-samples t-tests showed that there were no statistically significant clinical and paraclinical differences between the sub-group of patients with a history of cerebral ischemic events and those without any stroke or TIA, except for the score of the MMSE test, patients with a history of stroke had an MMSE score lower with 1.92 than those without a history of stroke (1.92, 95% CI, -1.09 to 4.93, p=.006). Even though statistical significance was not obtained for the other clinical and paraclinical variables, it is worth mentioning that when compared with patients without a history of cerebral ischemic events, patients with a history of stroke/TIA had more severe CA stenosis, lower scores of the CDT, higher values of fibrinogen and triglycerides blood levels, and lower hemoglobin and platelets number than those without a history of stroke/TIA (data are shown in Table 2).

	History of stroke & TIA	N	Mean	Standard deviation
Hemoglobin	No	9	14.2	2.02
	Yes	65	13.5	1.4
Platelet no.	No	9	227555.6	71337.4
	Yes	65	227496.9	52340
EGF	No	9	75.8	15.5
	Yes	65	76	22.2
Fibrinogen	No	9	337.7	53
	Yes	65	360.4	55.3
Total cholesterol	No	9	151.4	50
	Yes	65	148.4	49.8
Triglycerides	No	9	94.7	41.3
	Yes	65	117.6	61.5
BMI	No	9	29.2	4.2
	Yes	65	26.7	3.9
CDT	No	9	8.1	2.5
	Yes	65	7.7	2.9
Carotid artery stenosis	No	9	76.5	17.7
	Yes	65	85.3	18.6

TABLE 2. Descriptive data – differences between patients with/and without a history of stroke

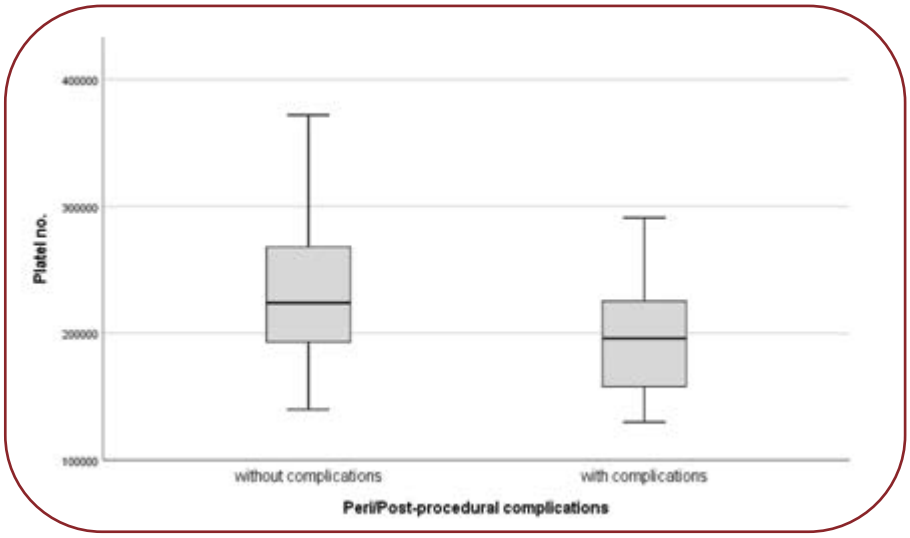

FIGURE 1. Peri- and post-procedural complications among studied patients

Differences between patients who developed complications after CAS *vs.* those with no complications after CAS

Independent-samples t-tests showed that there was a statistically significant difference in the mean number of platelets between patients who developed complications after CAS and patients who did not develop any kind of complications. These patients developed complications after CAS having 37 210 ± 1 648 fewer platelets than those who did not develop any kind of complications [t(72) = 2.304, p = .024]. No other significant differences were observed between the two

TABLE 3. Pearson correlation for CAS periprocedural complications

	r	*p*
Platelet no.	-.262*	.024

Note. *=statistically significant at p<.05 level, r=Pearson's correlation coefficient

TABLE 4. Logistic regression predicting the likelihood of developing complications during/after CAS based on hemoglobin, platelet no., EGF, fibrinogen, total cholesterol, and triglycerides

	B	SE.	Wald	Sig.	OR	95% CI.for EXP(B)	
						Lower	Upper
Hemoglobin	.115	.204	.318	.573	1.122	.752	1.675
Platelet no.	.000	.000	4.633	.031	1.000	1.000	1.000
EGF	-.005	.014	.119	.730	.995	.968	1.023
Fibrinogen	-.002	.006	.102	.749	.998	.987	1.009
Total cholesterol	.001	.006	.019	.891	1.001	.989	1.013
Triglycerides	-.002	.006	.131	.717	.998	.986	1.010

TABLE 5. Multiple regression results for CAS severity

	CAS severity	B	95.0% CI for B		SE B	β	R^2	Δ R^2	Sig
			LL	UL					
Model 1	Model						.22	.15	*.01*
	Constant	88.8	38.7	139	25.1				*.01*
	Haemoglobin	-1.6	-4.4	1.1	1.4	-1.4			*.24*
	Platelet no.	-4.4	0	0	0	-130			*.25*
	EGF	-0.6	-.26	.13	.1	-.07			*.52*
	Fibrinogen	.09	.02	.16	.04	.27			*.01*
	Total cholesterol	-.07	-.16	.012	.04	-.19			*.08*
	Triglycerides	.09	.02	.16	.04	.28			*.02*
Model 2	Constant	70.9	25.7	116.1	.28				*.00*
	Age	.33	-.24	.90	.29	.15			*.25*
	Gender	4.0	-6.3	14.5	5.23	.09			*.43*
	Hypertension	-14.3	-34.6	5.9	10.1	-.175			*.16*
	Type 2 diabetes	3.1	-7	13.2	5	.08			*.54*
	Chronic kidney disease	.07	-11.7	11.9	5.9	0			*.99*
	Atrial fibrillation	.6	-13.7	15.1	7.2	.01			*.92*
	Dislipidemia	-.2	-14	13.5	6.9	-.005			*.97*
	Obesity	-8.7	-20.6	3.2	5.9	-.18			*.15*

B=unstandardized regression coefficient, CI=confidence interval, LL=lower limit, UL=upper limit, SE B= standard error of the coefficient; β=standardized coefficient; R^2=coefficient of determination; Δ R^2=adjusted R^2

groups of patients. Further analysis showed that there was a small negative correlation between the number of platelets and the risk of having CAS periprocedural complications, (r = .-26, p<.05, results shown in Table 3).

Clinical and biological variables capable of predicting the occurrence of complications during or after CAS

Binomial logistic regression was performed to ascertain the effects of the number of platelets on

the likelihood that patients would develop complications after CAS. The logistic regression model was statistically significant, $\chi^2(1) = 4.633$, $p = .031$, but the sensitivity of the model was zero and the area under the ROC was .29, both suggesting that the number of platelets was not a good model for predicting complications after CAS in this group of patients. No other clinical or paraclinical parameter was able to predict the occurrence of complications during or after CAS (Table 4).

Role of demographical and paraclinical variables in the severity of carotid artery stenosis

A multiple regression test was run to predict the severity of CA stenosis from selected laboratory tests (hemoglobin, platelet number, fibrinogen, triglycerides, total cholesterol blood levels, and the estimated glomerular filtration rate). The multiple regression model statistically significantly predicted the severity of CAS, $F(6, 67) = 3.073$, $p < .05$, adj. $R2 = .146$. Only the levels of fibrinogen, total cholesterol, and triglycerides added statistically significantly to the prediction, $p < .05$. Regression coefficients and standard errors can be found in Table 5.

No other clinical characteristics (age, sex) were found to contribute to the severity of CA stenosis when performing multiple regression analysis.

Role of clinical and biological variables in the severity of neurocognitive impairment

A multiple regression test was also run to predict the severity of neurocognitive impairment assessed through MMSE and CDT from the same variables used for the prediction of CA stenosis. Except the presence of atrial fibrillation ($F1, 72) = 4.704$, $p < .05$, adj. $R2 = .048$), no other clinical or biological variable was found to contribute to the neurocognitive impairment severity (results shown in Table 6).

DISCUSSION

In the present study, the only statistically significant difference between patients with CA stenosis and history of stroke and those without a history of stroke was that subjects with a history of ischemic cerebro-vascular events had lower scores on the MMSE examination.

These results are under the well-known fact that stroke is a risk factor for developing neurocognitive impairment and that one-third of stroke survivors develop vascular dementia (VaD) (16). However, there was a statistically significant, highly positive correlation between the MMSE and the CDT scores ($r(72)= .72$, $p<0.05$) in our cohort, and there was no significant difference between the CDT scores in the two groups of patients. While several studies are suggesting that CDT is a useful screening tool for dementia (17-19), some authors believe that CDT is not sensitive enough for differentiating between patients with normal cognition and the ones with minor cognitive impairment (20, 21). This might also be the case in our patients, approximately 85% of the tested patients having mild cognitive impairment, with an MMSE score higher than 25. Moreover, given that most patients included in the study had a history of minor strokes in the ICA territory, it is possible that the perceptual-motor cognitive domain to have been less affected than other cognitive domains and thus, not affecting the CDT score as it would happen in a posterior cerebral artery stroke or a major stroke in the ICA territory. Besides, in our selected group of patients, independent of their history of stroke, those with a history of atrial fibrillation had lower MMSE scores than individu-

TABLE 6. Multiple regression results for MMSE score

MMSE score	B	95.0% CI for B		SE B	β	R^2	Δ R^2	Sig
		LL	UL					
Model						.061	.048	*.03*
Constant	27.1	26.1	28.209	.52				*.00*
Atrial fibrillation	-3	-5.8	-.25	1.4	-.24			*.03*

B=unstandardized regression coefficient, CI=confidence interval, LL=lower limit, UL=upper limit, SE B=standard error of the coefficient; β=standardized coefficient; R^2=coefficient of determination; Δ R^2=adjusted R^2

als who had normal cardiac rhythm. The influence of atrial fibrillation on cognition was assessed in several studies which concluded that AF was an independent risk factor not only for vascular dementia but also for other types of dementias, including the one associated with the Alzheimer's disease (22-24). An essential factor that was not assessed in our study was AF duration and anticoagulant treatment in each patient. These factors will be taken into consideration in the subsequent studies to investigate the long-term potential protective role of anticoagulants against neurocognitive impairment.

Even though for the other clinical and paraclinical variables, statistical significance was not obtained, it is worth to mention that, when compared with patients without a history of cerebral ischemic events, those who had a history of stroke/TIA had more severe CA stenosis, lower scores of the CDT, higher values of fibrinogen and triglyceride blood levels, and lower hemoglobin and platelets number than patients without a history of stroke/TIA.

An important finding in our group of patients was that specific biological parameters, more specifically hemoglobin, fibrinogen, total cholesterol, triglyceride blood levels, and also EGF, were found to shape an appropriate model for predicting the severity of CA stenosis. Nevertheless, the only factors which brought statistical significance to the predicting model were the blood fibrinogen and triglyceride levels. Both fibrinogen and triglycerides were incriminated in previous studies as being significant risk factors not only in early atherosclerotic changes of arterial vessels but also for the progression of CA stenosis, in developing "high-risk" carotid plaques and in increasing the overall risk of stroke (25-28). The critical aspect of our finding is that when considered together, fibrinogen and triglyceride levels can predict the risk of a patient having "high-grade" stenosis. This could be helpful for clinicians when deciding on performing or prescribing carotid artery ultrasound screening in asymptomatic patients with cardio- and cerebro-vascular risk factors.

On the final aspect of our registry-based study, when assessing the risk factors for developing CAS stenting peri- or post-procedural complications, we found that patients with a lower number of thrombocytes had a higher risk of developing complications than those with a higher count of thrombocytes. To our knowledge, this is the first study reporting such findings. To validate this finding, this will be further verified at the end of the study on a higher number of patients.

There are several limitations to the current study: more men than women were included in the study, even though patients were included consecutively; there are also more patients with symptomatic CA stenosis than those with asymptomatic arterial stenosis, and there was insufficient data regarding the type of carotid atheromatous plaques to analyze them. All these limitations could be corrected by including a higher number of patients and will be considered at the end of the study.

CONCLUSIONS

The present study brings essential information about a population that is more prone to cerebral ischemic events than that of most other countries. All data obtained so far and which will further result from analyzing the clinical, demographic, and biological features of patients included in this registry should be used for implementing populational strategies for preventing further strokes. Moreover, these results should also make the clinician consider personalizing, or delaying the treatment of patients with carotid artery stenosis depending on their clinical or biological profile, for avoiding unnecessary complications. ❑

Conflicts of interest: none declared.

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