

# Circadian patterns of ischemic stroke onset

<sup>1</sup>Dana M. Fodor, <sup>2</sup>Daniel Gongnanu-Nitu, <sup>2</sup>Lacramioara Perju-Dumbrava

<sup>1</sup> Department of Neurology, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania; <sup>2</sup> Department of Surgery, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania.

**Abstract.** Objective: The aims of our study are to investigate if the ischemic stroke and its subtypes follow a circadian pattern in occurrence in Cluj-Napoca area and to examine the existence of an association between the conventional risk factors and this circadian variation. Material and Method: Ischemic stroke data were collected from the Patient Records of a consecutive series of 969 patients admitted through Emergencies Room at Neurology Departments I and II of the District Hospital of Cluj-Napoca, between 1 January 2012 and 31 December 2012. The classifiable onset time was assigned to one of four six-hours intervals: 00.01- 06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon) and 18.01-24.00 (evening). Demographic data and vascular risk factors were recorded for each patient. Results: The circadian variation of onset for all ischemic stroke subtypes was shown by descriptive analysis and confirmed by Fourier spectral analysis, with the peak of occurrence in the morning hours and the lowest occurrence during nighttime. The Fourier analysis showed the presence of two cycles of 12 and of 24 hours. The descriptive analysis and estimated odd ratio, for the occurrence of ischemic stroke for each of the four six-hours interval regarding the association with the risk factors, did not revealed any influence of them in the circadian pattern of ischemic stroke onset. The mortality for the ischemic stroke occurred in the afternoon hours has an odd ratio of 0.22 with a p value of 0.011. Conclusion: The cerebro-vascular events are not randomly distributed over time, but have a peculiar distribution along the day, following a circadian variation with the higher incidence in the morning and the lower in the night. This circadian pattern is independent by demographic data, vascular risk factors and history of previous stroke.

**Key Words:** ischemic stroke onset, circadian variation, ischemic stroke subtypes

**Copyright:** This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Corresponding Author:** D.M. Fodor, e-mail: fodordana@yahoo.com

## Introduction

In the recent literature the concept of the temporal pattern for distribution of the cerebro-vascular events onset, besides the one of the cardio-vascular events, became more obvious. The similarity between the patterns of diurnal variation of the two types of pathology, regarding their onset time, suggests that cerebro-vascular and cardio-vascular events share common triggering factors (LeBlanc 2014 Shaw et al 2009, Terayama 2013, Turin et al 2009).

Even if the diurnal pattern of ischemic stroke (IS) onset was established, data regarding the chronological variation of stroke subtypes are limited (Casetta et al 2002, Turin et al 2009) and only a few have reported the relationship between this circadian pattern and the conventional vascular risk factors (Ali et al 2011, Casetta et al 2002, Turin et al 2009). Knowledge about any periodicity in IS occurrence may provide clues for primary and secondary prevention and treatment.

The objective of this study are to examine the existence of a circadian pattern in IS occurrence and the association between it and vascular conventional risk factors and whether there are differences in this temporal variation regarding ischemic stroke subtypes.

## Material and Method

In our retrospective, hospital – based study, we included a consecutive series of 969 patients with IS admitted between 1 January 2012 and 31 December 2012 through Emergency Room

to Neurology Department I and II of the District Hospital of Cluj-Napoca (which serve the population of Cluj-Napoca City and of the surroundings). The Cluj-Napoca Metropolitan Area has a population of 411.379 inhabitants (Cluj County Regional Statistics 2013).

The diagnosis of stroke was defined, according to World Health Organization criteria, as rapidly developing clinical symptoms or signs of focal or global loss of cerebral function with symptoms lasting more than 24 h or leading to death, with no apparent cause other than vascular origin (WHO 1989) and was made by a neurologist. For each patient we recorded demographic data (gender, age), date of onset and the day-time interval/hour where was specified, risk factors and comorbidities (hypertension (with or without previous treatment), diabetes mellitus, hypercholesterolemia, coronary artery disease (CAD), atrial fibrillation (AF), smoking status, history of previous transient ischemic attack (TIA) or stroke, type of stroke and mortality during hospitalization treatment). Lack of computed tomography in the first 48 hours and of the date of stroke onset at least was exclusion criteria. The stroke subtypes were diagnosed according The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria (Adams et al 1993), the most widely used classification of ischemic stroke, in the following subtypes according to its etiology: 1) large-artery atherosclerosis (embolus/thrombosis) 2) cardio-embolism, 3) small-vessel occlusion (lacune), 4) stroke of other determined etiology and 5) stroke of undetermined etiology (two or more causes identified/ negative evaluation/ incomplete evaluation). Diagnoses were based on

clinical characteristics and on results of diagnostic tests such as brain imaging (CT/MRI), cardiac imaging (echocardiography), vascular imaging (duplex imaging of extra-cranial arteries, arteriography) and laboratory assessments for a pro-thrombotic state. Precise or approximately determination of the hour or at least the interval of symptoms onset was possible for 820 and was assigned to one of four six-hours intervals: 00.01- 06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon) and 18.01-24.00 (evening), arriving from the information available for each patient in Patient Records. For the remaining 149 patients the date of stroke onset could be determined. The wake-up stroke (the situation when the symptoms of stroke was first recognized to the wake-up moment) were assigned equally between 00.01-06.00 (night) and 06.01-12.00 (morning).

Statistical analyses were performed using Excel Microsoft and SPSS software v. 17. The incidence of IS measured across the time intervals and presented as proportions (P) with CI calculated using Wilson’s method (CI 95% =  $P \pm 1.96 * (P(1-P)/N)^{1/2}$ ). The circadian rhythm was analyzed using Fourier spectral analysis to identify any significant rhythms that might be occurring and subsequent linear regression for modeling a cosinor function for 12 and 24 hour periods. Multimodal logistic regression analysis was performed on data (IS as global variable) with the time blocks modeled as dependent variable (time point 00.01 –06.00 as reference category) and OR coefficients were estimated for morning, afternoon, evening and undetermined interval. The risk factors were modeled as independent variable to calculate the respective odds. The significance threshold 0.05 was considered for all statistical analysis.

## Results

The demographic characteristics of the patients with IS are shown in table 1. The man is counting for 53.63% (510 patients) and women for 47.37 % (459 patients). The average age of women is 72.76+/-10.79 year comparing with that of man which is 69.04+/-11.2 year.

The total of 969 patients was classified, according TOAST criteria in: 60 patients with IAT (6.2%), 153 patients with IE (15.8%), 538 patients with IL (55.5%), 7 patients with of IO (other determined etiology) (1%) and 211 patients with IU (21.8%) (figure 1). For the next statistical analysis the patients with IO were excluded because of their heterogenic etiology (4 patients diagnosed with stroke in the context of paraneoplastic syndrome, 1 patient with cerebral infarct secondary to cerebral metastasis of breast cancer, 1 patients with cerebral vascular malformation and 1 patient with infarct caused by common carotid artery dissection).

Table 1. The demographic characteristics of the patients with ischemic stroke stratified by subtypes

Age	M mean (SD)	F mean (SD)
IAT	63.8 (10.9)	66.7 (12.5)
IE	74.8 (8.2)	77.4 (7.9)
IL	68.9 (11.3)	72.5 (10.4)
IU	68 (11)	70.8 (12.1)
<b>Total</b>	69 (11.2)	72.8 (10.8)

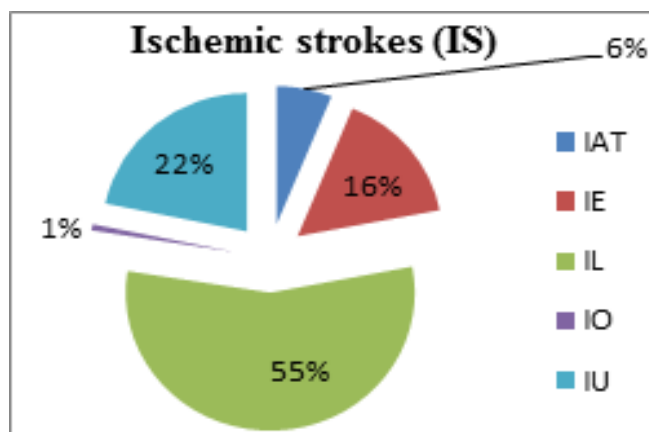


Figure 1: The percentage classification of ischemic stroke subtypes

The description of the circadian pattern of variation is illustrated in the figure 2 for all ischemic strokes and for each subtype onset along the day, concerning the four six-hours intervals convened. It shows an evident peak during the morning hour (corresponding to interval 06.01-12.00), followed by a slow decrease during afternoon (12.01-18.00) and evening (18.01-24.00) and a trough during nighttime (interval 00.01-06.00) for each type of stroke. The percentage of occurrence during the four six-hour intervals for each subtype is described in table 2.

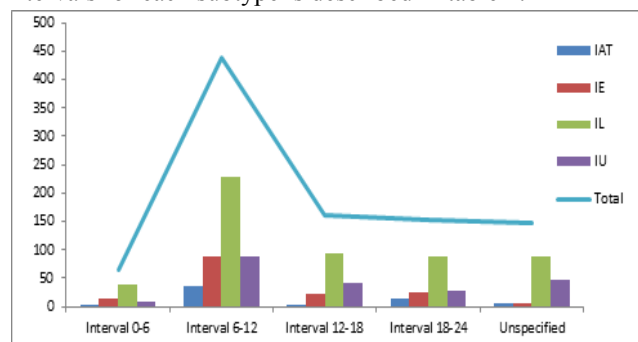


Figure 2: The distribution of stroke subtypes onset over the four six-hour intervals during the day.

Using the Fourier spectral analysis for the detection of the hypothesized circadian rhythmicity (cosinor function), after the random distribution along the daytime of the patients with undetermined onset time, we found two cycles of 24 and 12 hours for IS (shown in Figure 3) and for IS subtypes (not mentioned here, being similar). The cosinor indices for 24 hours cycle, for each stroke subtype, are summarized in the table 3.

The total of ischemic stroke and its subtypes was stratified by the presence of risk factors and comorbidities: anterior TIA/stroke, arterial hypertension, DM, hypercholesterolemia, CAD, AF and smoking status. Concerning the risk factors and comorbidities, the proportion of each IS subtype is described in the table 4, the circadian variation of IS is illustrated in figure 4 (first boxes) and the relationship between odd ratios values (OR) for the occurrence during each four six-interval of daytime is shown in figure 4 (second boxes). The time interval 00.01 – 06.00 was considered as reference category. For OR of all risk factors and comorbidities we found a p value >0.05. The same representation was made for age and gender, with the circadian variation of IS in figure 5 (first boxes) and the relationship between odd

Table 2. The proportion of each stroke subtype assigned to the four six-hour intervals

Stroke type	Night (0-6)	Morning(6-12)	Afternoon(12-18)	Evening (18-24)
IAT	5% (-0.5-10.5)	58.3% (45.9-70.8)	5% (-0.5-10.5)	21.7% (11.2-32.1)
IE	9.2% (4.5-13.7)	57.5% (49.7-65.3)	13.7% (8.3-19.2)	15.7% (10.0-21.4)
IL	7.3% (0.5-9.4)	42.4% (38.2-46.6)	17.7% (14.4-20.9)	16.4% (13.2-19.5)
IU	3.8% (1.2-6.3)	41.2% (34.6-47.9)	19.4% (14.0-19.0)	13.3% (8.7-17.8)

Table 3. The parameters from Fourier analysis (cosinor) of 24 hours rhythmicity

Stroke Type	F	p	Mesor	Amplitude	Acrophase
IAT	9.201	0	0.04	0.03	12.37
IE	30.553	0	0.1	0.09	12.52
IL	54.875	0	0.3	0.2	13.44
IU	21.033	0	0.1	0.1	14.26

Table 4. The presence of risk factors among the patients with ischemic stroke

Risk factor	IAT %	IE %	IL %	IU %	Total IS %
Hypertension	86.7(78.0-95.2)	96.7(93.9-99.5)	89.4(88.0-93.0)	85.8(81.0-90.5)	89(88.3-92.2)
Diabetes Mellitus	21.7(11.2-32.1)	22.2(9.0-20.2)	23.2(21.4-25.0)	24.2(18.4-29.9)	24(21.5-26.9)
Hypercholesterolemia	50(37.3-62.7)	21.6(15.0-28.1)	39(34.9-43.2)	23.7(18.0-29.5)	36.9(34.2-40.3)
CAD	33(21.4-45.2)	47(39.1-54.9)	55.5(51.3-59.7)	33.1(26.8-39.5)	37.6(34.7-40.9)
AF	23.3(12.6-28.6)	85.6(82.7-92.2)	15.8(22.7-18.8)	3(1.8-0.4)	25(22.8-28.3)
Smoking habit	13.3(4.7-21.9)	3.3(0.4-6.1)	4.7(42.9-51.3)	11.4(0.7-15.6)	7.2(5.6-8.9)
Previous TIA/stroke	26.7(15.5-37.6)	27.8(20.4-33.2)	22(20.0-27.2)	21.8(16.2-27.3)	23.8(21.3-26.7)

ratios values (OR) for the occurrence in man/women and for <65 years/ >65 years during each four six-interval of daytime is shown in figure 5 (second boxes).

The circadian variation of stroke mortality during hospitalization is shown in figure 6. The OR coefficients were estimated and represented graphically for each time interval concerning the mortality during hospitalization considering the time interval 00.01 – 06.00 as reference category. A value of  $p=0.011$  was found for afternoon (12.01-18.00 interval) (Figure 6 and 7).

## Discussion

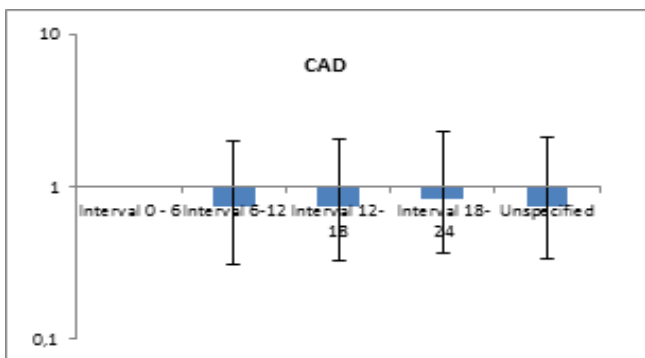
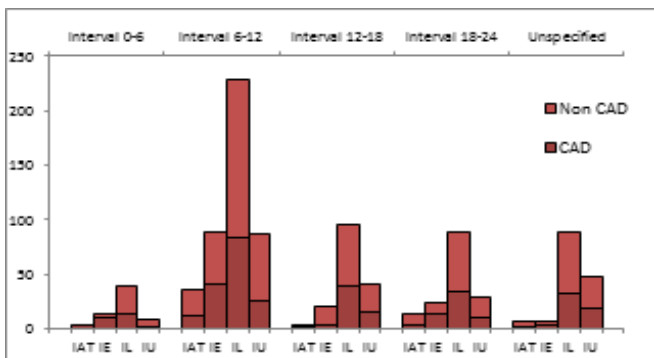
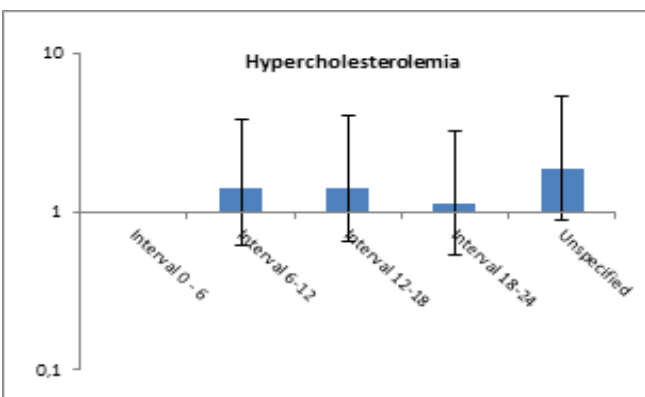
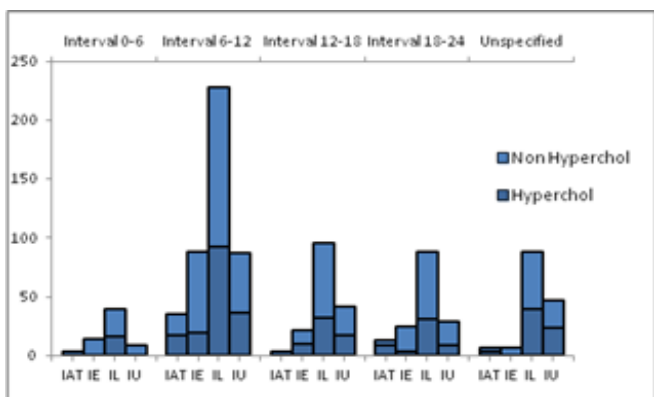
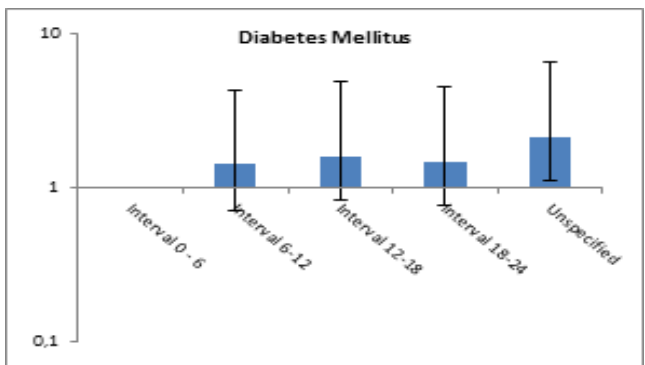
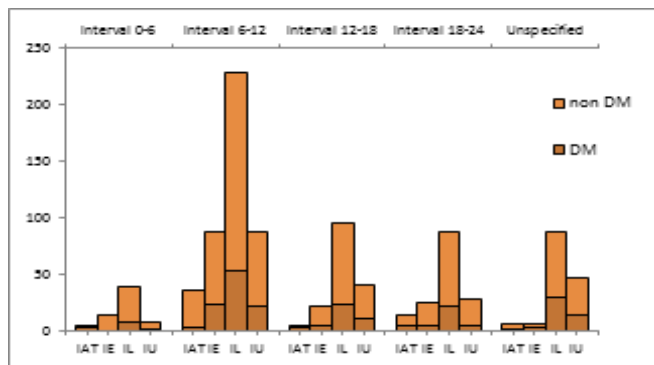
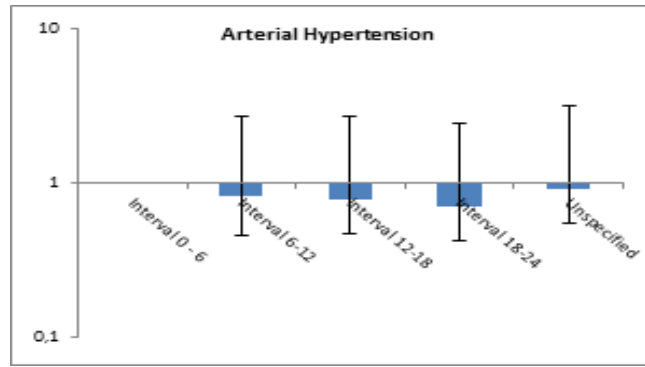
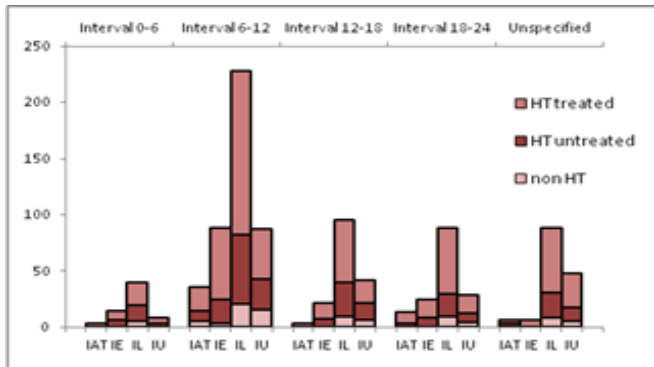
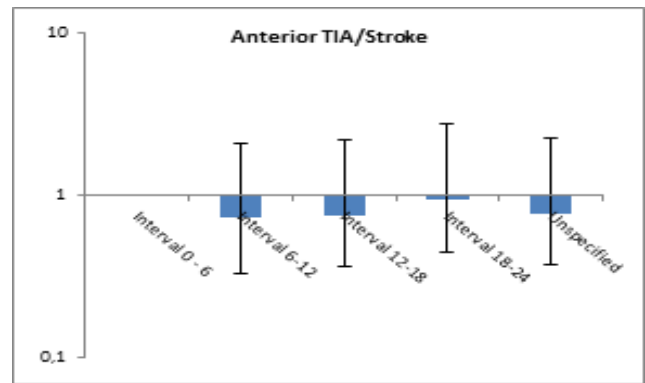
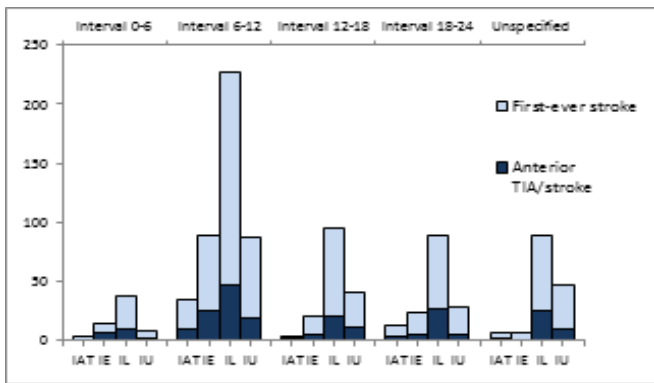
The proportion between the five subtypes of stroke found in our study is relatively different by other reports, with a higher proportion of IL – 55% in comparison with 15-25% described in the literature. A possible explanation is the high prevalence of the known risk factors for IL between our patients with IS, especially arterial hypertension (89% from total IS and 89.4% from IL) and diabetes mellitus (24% from all IS and 23.2 from IL) (Bailey et al 2012). The lower proportion of IAT (only 6% in comparison with 13-21% reported) and of IE (16% in comparison with 25-30%) is due by a relative high number of patients with evidence of both cardio-embolic source and significant stenosis (>50%)/occlusion of a major brain artery or branch cortical artery, this cases being included in the IU category (22% in our study in comparison with 30-33% (figure 1) (Palm et al 2012). Overall the men age is about 3.5 years lower than the age of women, obvious for all stroke subtypes, reflecting the appearing or worsening of the existing vascular risk factors after menopause installation (table 1) (Bushnell 2008).

Our results regarding the circadian rhythmicity of ischemic stroke are in accordance with the findings of previous reports

available in the literature, with the highest incidence of occurrence during 06.01-12.00 noon and the minimum occurrence during the night (00.01-06.00) (Butt et al 2009, Manfredini et al 2005, Tsai et al 2013, Turin et al 2009, Wouters et al 2014), for all ischemic stroke subtypes (Casetta et al 2002, Spengos et al 2003, Turin et al 2009), including IL for which other authors have reported a highest occurrence during nighttime (Castilla-Guerra et al 2009, Naess et al 2011) (figure 2 and table 2).

There are previous studies which indicate a single peak in the morning (Gupta et al 2005, Manfredini et al 2005) and others showing a double peak of circadian variation for all IS or for some of IS subtypes, with a second, less impressive, peak in the afternoon (Casetta et al 2002, Omama et al 2006, Turin et al 2012). Their study methodology was based on the division of the daytime in more than four intervals (as in our study): six 4-hours, twelve 2-hours or even 24 1-hours. The data about the patients with stroke from their Stroke Registries were more accurate and permitted an increased precision in the stroke onset time determination and consequently the possibility to obtain a more detailed pattern of the IS diurnal rhythmicity.

We found this pattern, with significant increase of IS occurrence during morning hours, even in the settings of equally distribution of the wake-up stroke number between the night and the morning interval, related by the fact that there are opinions that the stroke “concentration” at the time of awakening is not due by the “concentration” of stroke occurrence, but to that of its recognition (Omama et al 2006, Wouters et al 2014). Regarding IS, the wake-up strokes count for 9.5% in comparison with 20-25% reported (Omama et al 2006, Rimmele et al 2014, Wouters et al 2014).



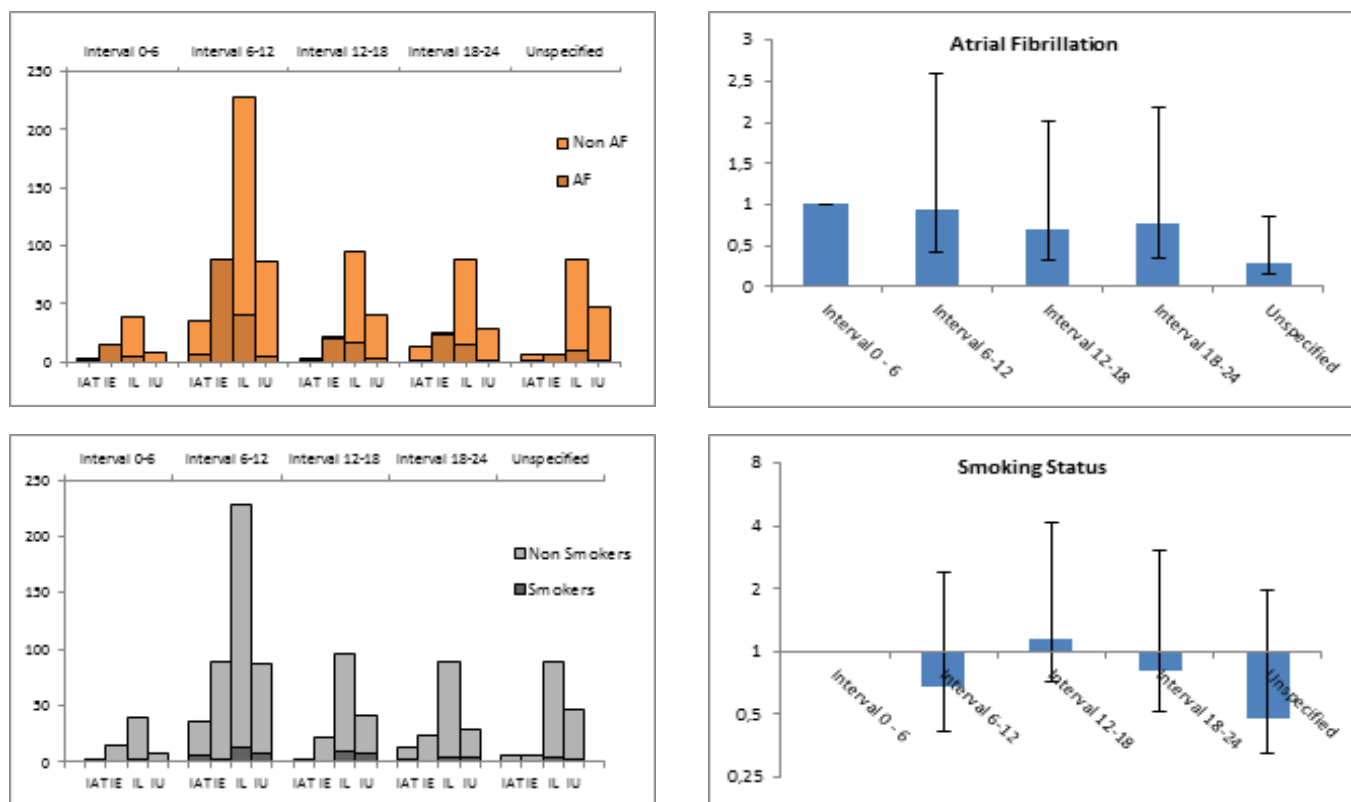


Figure 4: The circadian variation (first boxes) and the relationship between the odds ratio coefficients (OR), (considering time interval 00.01 – 06.00 as reference category) (second boxes) for the occurrence of ischemic stroke stratified by the presence of risk factors and comorbidities: anterior TIA/stroke, arterial hypertension, diabetes mellitus (DM), hypercholesterolemia, coronary artery disease (CAD), atrial fibrillation (AF) and smoking status.

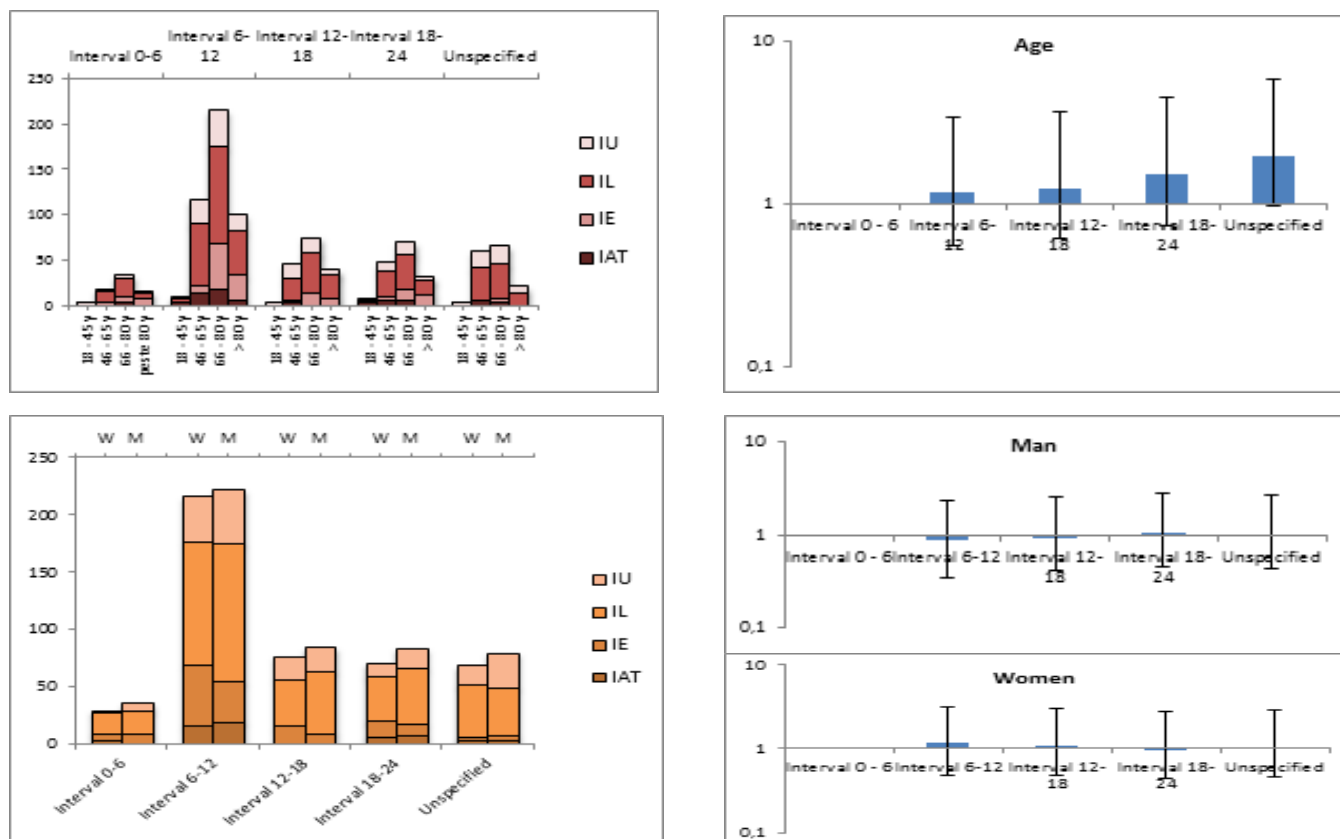


Figure 5: The circadian variation (first boxes) and the relationship between the odds ratio coefficients (OR), (considering time interval 00.01 – 06.00 as reference category) (second boxes) for the occurrence of ischemic stroke concerning age and gender (y-years, M-man, W-women)

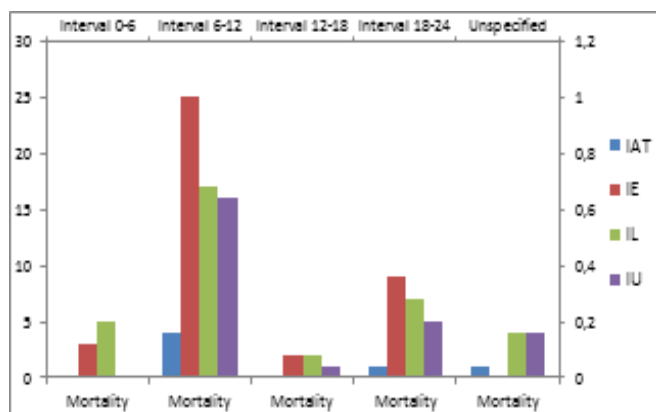


Figure 6: The mortality during hospitalization concerning the four six-hours intervals and ischemic stroke subtypes.

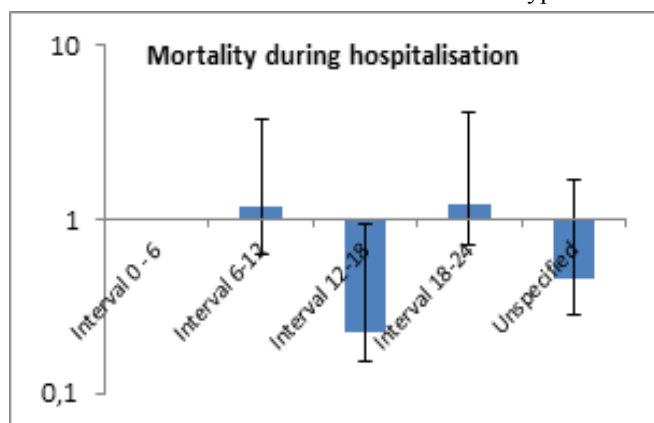


Figure 7: The OR representation for each four six-hour interval concerning mortality during hospitalization (considering the time interval 00.01 – 06.00 as reference category)

The spectral Fourier analysis of the hypothesized circadian variation onset of IS has exhibited the existence of two cycles: one of 12-hours and one of 24-hours. Arriving from the graphic and indices (figure 3 and table 4), we can speculate that the two cycles are phase-shifted by approximately 90 degree. The analysis of the 24 cosinor curve shows a hall-mark of the 12-hours cycle in its first part. Initially the two cycles are antagonizing each other and after 12-hours are synchronizing (producing a synergic effect) leading to the probability in our opinion of the existence of a protective mechanism against stroke in the 00.01-06.00 interval. The hypothesis arising from this analysis is that the nocturnal sleep protect against stroke, despite the old traditional teaching that strokes are more likely to occur at night (Lago et al 1998), but it needs more studies for confirmation. The circadian rhythmicity in IS occurrence appears to be independent by the demographic factors: gender and age (figure 5) and the history of the known risk factors (figure 4). This affirmation is suggested by the observed similar pattern of circadian variation for each stroke subtypes in the condition of presence and absence of the mentioned risk factors and comorbidities (first boxes of figure 4), sex and age categories (first boxes of figure 5). The estimated odd ratio (OR) values for the occurrence of IS for each interval, concerning age and sex were  $<1$  for age and for man and were  $>1$  for women, but with a p values  $>0.05$  (considered as statistical significance threshold).

Concerning the vascular risk factors, the estimated OR were  $<1$  for previous TIA/stroke, hypertension, CAD, AF and smoking habit and  $>1$  for diabetes mellitus and hypercholesterolemia, but without statistical significance for none of them (figure 4, second boxes). This finding is in accordance with other studies which showed no difference in the pattern of stroke onset between the patients with or without risk factors (Casetta et al 2002, Turin et al 2012).

The conclusion that none of the common risk factors seems to have a contribution to the circadian variation of IS onset suggests that it may be triggered by other unknown factors, intrinsic for the morning hours. Probably the mechanism implies the diurnal rhythmicity of a series of biologic factors such as blood pressure (with physiological nocturnal decrease and morning increase), hemostatic balance (with increased platelet aggregability, hypercoagulability, hypofibrinolysis, and increases levels of hematocrit with hyperviscosity of the blood in the morning), autonomic system activity (with activation of the sympathetic nervous system after the wake-up moment with consequence on vascular tone, BP, heart rate). The diurnal rhythmicity of the mentioned endogenous factors depend partially by the day-night cycle of the physical activity and the assumption of the up-right posture (as exogenous factors) associated with the awaking moment (Atkinson et al 2010, Chrusciel et al 2009, Kario et al 2010, LeBlanc 2014, Turin et al 2012). Taking the example of BP (the best studied risk factor for cardio-vascular and cerebro-vascular events), in our study the patients normotensive and hypertensive with and without anti-hypertensive medication had the same circadian variation of IS onset (figure 4). It suggest that the BP diurnal rhythmicity (related partially by the abrupt shifting from the absence of physical activity during sleep to sudden physical activity on awaking and arising moment, via sympathetic activation) and not BP itself, play an important role in the circadian chronobiology of the IS including its onset. We have to mention that for the most patients, we did not have information about their schedule of anti-hypertensive medication. There are data that bedtime antihypertensive drugs administration in comparison with conventional after-awaking treatment is more effective in the control of BP and significantly decrease the cardio-vascular morbidity (Hermida et al 2010). There are reports suggesting the modification of the circadian rhythm of BP post ischemic stroke (with decrease/increase of the nocturnal BP decline, as a triggering factor for IS occurrence) but we did not found a more impressive peak in the morning for the patients with previous stroke in comparison with the patients with the first-ever stroke (Figure 3) (Castilla-Guerra et al 2011, Kwon et al 2014). Analyzing the aspect of mortality during hospitalization, it count for 10.9% from the total of IS in our study. The higher proportion of mortality was observed between the patients with IE (25.5%) related probably by the increased extension of this subtype of stroke. The lower mortality (6.5%) was recorded for IL, the infarct extension and clinical picture being less severe. We found a mortality frequency of 10% for IAT and 12.3% for IU, all in accordance with the data from the literature (de Jong et al 2003, Turin et al 2012). Regarding the circadian variation of IS subtypes mortality the pattern follow the one of IS onset (figure 6). Interestingly, analyzing the estimated OR values for each four intervals described in figure 7 we can speculate

a “protective effect” against mortality during hospitalization for the stroke occurred in the afternoon (12.01-18.00), with a  $p=0.011$  (considering the time interval 00.01 – 06.00 as reference category).

The highest incidence of stroke in the morning has a sociological dimension as information, with practical implication for the current and future treatment for the patients with IS. The hospitals / units that propose to treat IS patients require a higher level of awareness and availability during morning hours. The intra-venous or intra-arterial thrombolysis treatment seems to have better outcome during diurnal compared with nocturnal period (Vilas *et al* 2012). Another broad implication of the circadian variation of IS onset may be a preventive one, by treating the risk factors concerning their circadian variation too. We can suppose that a chrono-therapeutic approach may be useful for arterial hypertension (Hermida *et al* 2010), especially for the BP morning surge and the situation with decrease of the physiological nocturnal decline of BP (non-dipper and reverse-dipper profile) and even in the case of antiaggregant/anticoagulant treatment targeting the concurrent morning pro-thrombotic condition (Haus 2007).

## Conclusions

By our knowledge, this is the first Romanian study regarding the circadian variation of ischemic stroke onset concerning its subtypes too. Our results show that ischemic stroke and its subtypes have a circadian variation with the highest peak in the morning and the lowest occurrence during nighttime. The mortality due to ischemic stroke follows the same circadian variation. This pattern of variation is independent by the presence of conventional vascular risk factors (arterial hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, atrial fibrillation and smoking status), by previous stroke and by demographic factors, suggesting that the circadian rhythmicity of endogenous factors, influenced by the day-night cycle of physical activity, not strictly risk factors itself, play a role in the circadian pattern of stroke occurrence. This founding may lead to therapeutic implications regarding the treatment with acute interventions like thrombolysis and the chrono-therapeutic approach of the chrono-risk factors of ischemic stroke.

## References

Adams HP Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, *et al*. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24(1):35-41.

Ali K, Leong KM, Houlder S, Getov S, Lee R, Rajkumar C. The relationship between dipping profile in blood pressure and neurologic deficit in early acute ischemic stroke. *Journal of Stroke and Cerebrovascular Diseases* 2011;20(1):10-5.

Atkinson G, Jones H, Ainslie PN. Circadian variation in the circulatory responses to exercise: relevance to the morning peaks in strokes and cardiac events. *European Journal of Applied Physiology* 2010;108(1):15-29.

Bailey EL, Smith C, Sudlow CL, Wardlaw JM. Pathology of lacunar ischemic stroke in humans--a systematic review. *Brain Pathol* 2012;22(5):583-91.

Bushnell CD. Stroke and the female brain. *Nature Clinical Practice Neurology* 2008;4(1):22-33.

Butt MU, Zakaria M, Hussain HM. Circadian pattern of onset of ischaemic and haemorrhagic strokes, and their relation to sleep/wake cycle. *JPMMA The Journal of the Pakistan Medical Association* 2009;59(3):129-32.

Casetta I, Granieri E, Fallica E, la Cecilia O, Paolino E, Manfredini R. Patient demographic and clinical features and circadian variation in onset of ischemic stroke. *Archives of Neurology* 2002;59(1):48-53.

Castilla-Guerra L, Espino-Montoro A, Fernandez-Moreno MC, Lopez-Chozas JM. Abnormal blood pressure circadian rhythm in acute ischaemic stroke: are lacunar strokes really different? *International Journal of Stroke* 2009;4(4):257-61.

Castilla-Guerra L, Fernandez-Moreno Mdel C, Espino-Montoro A, Lopez-Chozas JM. Nocturnal hypotension in patients after ischemic stroke: does it really matter? *European Journal of Internal Medicine* 2011;22(5):501-4.

Chrusciel P, Goch A, Banach M, Mikhailidis DP, Rysz J, Goch JH. Circadian changes in the hemostatic system in healthy men and patients with cardiovascular diseases. *Medical science monitor: international medical journal of experimental and clinical research* 2009;15(10):RA203-8.

Gupta A, Shetty H. Circadian variation in stroke - a prospective hospital-based study. *International Journal of Clinical Practice* 2005;59(11):1272-5.

Haus E. Chronobiology of hemostasis and inferences for the chronotherapy of coagulation disorders and thrombosis prevention. *Advanced Drug Delivery Reviews* 2007;59(9-10):966-84.

Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. *Chronobiology International* 2010;27(8):1629-51.

de Jong G, van Raak L, Kessels F, Lodder J. Stroke subtype and mortality. a follow-up study in 998 patients with a first cerebral infarct. *Journal of clinical epidemiology* 2003;56(3):262-8.

Kario K, Yano Y, Matsuo T, Hoshida S, Eguchi K, Shimada K. Additional impact of morning haemostatic risk factors and morning blood pressure surge on stroke risk in older Japanese hypertensive patients. *European Heart Journal* 2010;32(5):574-80.

Kwon HS, Lim YH, Kim HY, Kim HT, Kwon HM, Lim JS, *et al*. Association of ambulatory blood pressure and heart rate with advanced white matter lesions in ischemic stroke patients. *American Journal of Hypertension* 2014;27(2):177-83.

Lago A, Geffner D, Tembl J, Landete L, Valero C, Baquero M. Circadian variation in acute ischemic stroke: a hospital-based study. *Stroke* 1998;29(9):1873-5.

LeBlanc S. Circadian Rhythm in Stroke – The Influence of Our Internal Cellular Clock on Cerebrovascular Events. *Journal of Clinical & Experimental Pathology* 2014;04(02).

Manfredini R, Boari B, Smolensky MH, Salmi R, la Cecilia O, Maria Malagoni A, *et al*. Circadian variation in stroke onset: identical temporal pattern in ischemic and hemorrhagic events. *Chronobiology International* 2005;22(3):417-53.

Naess H, Idicula T, Brogger J, Waje-Andreassen U, Thomassen L. High proportion of lacunar strokes at night: the Bergen stroke study. *Journal of Stroke and Cerebrovascular Diseases* 2011; 20(5):424-8.

Omama S, Yoshida Y, Ogawa A, Onoda T, Okayama A. Differences in circadian variation of cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage by situation at onset. *Journal of Neurology, Neurosurgery, and Psychiatry* 2006;77(12):1345-9.

Palm F, Urbanek C, Wolf J, Buggle F, Kleemann T, Hennerici MG, *et al*. Etiology, risk factors and sex differences in ischemic stroke in the Ludwigshafen Stroke Study, a population-based stroke registry. *Cerebrovascular Diseases* 2012;33(1):69-75.

- Rezultate definitive ale Recensământului Populației și Locuitorilor - 2011 - analiza. Cluj County Regional Statistics Directorate Epub 2013-07-05.
- Rimmele DL, Thomalla G. Wake-up stroke: clinical characteristics, imaging findings, and treatment option - an update. *Frontiers in Neurology* 2014;5:35.
- Shaw E, Tofler GH. Circadian rhythm and cardiovascular disease. *Current Atherosclerosis Reports* 2009;11(4):289-95.
- Spengos K, Vemmos KN, Tsvigoulis G, Synetos A, Zakopoulos NA, Zis V, et al. Two-peak temporal distribution of stroke onset in Greek patients. a hospital-based study. *Cerebrovascular Diseases* 2003;15(1-2):70-7.
- Terayama Y. Circadian rhythm and stroke. *Nihon Rinsho Japanese Journal of Clinical Medicine* 2013;71(12):2130-4.
- Tsai CF, Thomas B, Sudlow CL. Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. *Neurology* 2013;81(3):264-72.
- Turin TC, Kita Y, Rumana N, Nakamura Y, Takashima N, Ichikawa M, et al. Is there any circadian variation consequence on acute case fatality of stroke? Takashima Stroke Registry, Japan (1990-2003). *Acta neurologica Scandinavica* 2012;125(3):206-12.
- Turin TC, Kita Y, Rumana N, Takashima N, Ichikawa M, Sugihara H, et al. Morning surge in circadian periodicity of ischaemic stroke is independent of conventional risk factor status: findings from the Takashima Stroke Registry 1990-2003. *European journal of neurology* 2009;16(7):843-51.
- Vilas D, Gomis M, Blanco M, Cortes J, Millan M, Perez de la Ossa N, et al. Circadian rhythms in the efficacy of intravenous alteplase in patients with acute ischemic stroke and middle cerebral artery occlusion. *Chronobiology International* 2012;29(10):1383-9.
- WHO. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke* 1989;20(10):1407-31.
- Wouters A, Lemmens R, Dupont P, Thijs V. Wake-up stroke and stroke of unknown onset: a critical review. *Frontiers in Neurology* 2014;5:153.

## Authors

- Dana M. Fodor, Department of Neurology, “Iuliu Hatieganu” University of Medicine and Pharmacy, 43th Victor Babes Street Cluj Napoca, Romania; email: fodordana@yahoo.com
- Daniel Gonganau-Nitu, Department of Surgery, Surgery Clinic No 1, “Iuliu Hatieganu” University of Medicine and Pharmacy; email: daniel.gonganau@gmail.com
- Lacramioara Perju-Dumbrava, Department of Neurology, “Iuliu Hatieganu” University of Medicine and Pharmacy, 43th Victor Babes Street, Cluj Napoca, Romania; email: lperjud@gmail.com

**Citation** Fodor DM, Gonganau-Nitu D, Perju-Dumbrava L. Circadian patterns of ischemic stroke onset. *HVM Bioflux* 2014;6(3):132-139.

**Editor** Stefan C. Vesa

**Received** 17 September 2014

**Accepted** 1 October 2014

**Published Online** 1 October 2014

**Funding** None reported

**Conflicts/  
Competing  
Interests** None reported